Biomedicine & Pharmacotherapy 142 (2021) 112018

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Tomato (*Solanum lycopersicum* L.) seed: A review on bioactives and biomedical activities

Manoj Kumar [a,*], Maharishi Tomar [b,*], Deep Jyoti Bhuyan [c], Sneh Punia [d], Simona Grasso [e], Amanda Gomes Almeida Sá [f], Bruno Augusto Mattar Carciofi [f], Fátima Arrutia [g], Sushil Changan [h], Radha [i], Surinder Singh [j], Sangram Dhumal [k], M. Senapathy [l], Varsha Satankar [m], T. Anitha [n], Anshu Sharma [o], R. Pandiselvam [p], Ryszard Amarowicz [q], Mohamed Mekhemar [r,*]

[a] Chemical and Biochemical Processing Division, ICAR - Central Institute for Research on Cotton Technology, Mumbai 400019, India
[b] Seed Technology Division, ICAR - Indian Grassland and Fodder Research Institute, Jhansi 284003, India
[c] NICM Health Research Institute, Western Sydney University, Penrith, NSW 2751, Australia
[d] Department of Food, Nutrition, & Packaging Sciences, Clemson University, Clemson, SC 29634, USA
[e] School of Agriculture, Policy and Development, University of Reading, Reading, UK
[f] Department of Chemical Engineering and Food Engineering, Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil
[g] Laboratory of Bioengineering, Earth and Life Institute-Applied Microbiology, Université catholique de Louvain, Croix du Sud, 2 - L7.05.19, B-1348 Louvain-la-Neuve, Belgium
[h] Division of Crop Physiology, Biochemistry and Post-Harvest Technology, ICAR-Central Potato Research Institute, Shimla 171001, India
[i] School of Biological and Environmental Sciences, Shoolini University of Biotechnology and Management Sciences, Solan 173229, Himachal Pradesh, India
[j] Dr. S.S. Bhatnagar University Institute of Chemical Engineering and Technology, Panjab University, Chandigarh 160014 India
[k] Division of Horticulture, RCSM College of Agriculture, Kolhapur 416004, Maharashtra, India
[l] Department of Rural Development and Agricultural Extension, College of Agriculture, Wolaita Sodo University, Wolaita Sodo, Ethiopia
[m] Ginning Training Centre, ICAR—Central Institute for Research on Cotton Technology, Nagpur 440023, India
[n] Department of Postharvest Technology, Horticultural College and Research Institute, Periyakulam 625604, Tamil Nadu, India
[o] Department of Food Science and Technology, Dr. Y.S. Parmar University of Horticulture and Forestry, Nauni 173230, India
[p] Division of Physiology, Biochemistry and Post-Harvest Technology, ICAR-Central Plantation Crops Research Institute (CPCRI), Kasaragod 671124, Kerala, India
[q] Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland
[r] Clinic for Conservative Dentistry and Periodontology, School of Dental Medicine, Christian-Albrecht's University, 24105 Kiel, Germany

ARTICLE INFO

Keywords:
Tomato seeds
Phytochemicals
Biological activities
Health promoting effects

ABSTRACT

The processing of tomato fruit into puree, juices, ketchup, sauces, and dried powders generates a significant amount of waste in the form of tomato pomace, which includes seeds and skin. Tomato processing by-products, particularly seeds, are reservoirs of health-promoting macromolecules, such as proteins (bioactive peptides), carotenoids (lycopene), polysaccharides (pectin), phytochemicals (flavonoids), and vitamins (α-tocopherol). Health-promoting properties make these bioactive components suitable candidates for the development of novel food and nutraceutical products. This review comprehensively demonstrates the bioactive compounds of tomato seeds along with diverse biomedical activities of tomato seed extract (TSE) for treating cardiovascular ailments, neurological disorders, and act as antioxidant, anticancer, and antimicrobial agent. Utilization of bioactive components can improve the economic feasibility of the tomato processing industry and may help to reduce the environmental pollution generated by tomato by-products.

1. Introduction

Tomato (*Solanum lycopersicum* L.) seed waste, which is approximately 5–10% tomato pomace, is generated during the processing of the tomato-based products and is a rich source of nutritional compounds, including proteins, amino acids, fatty acids, fiber, and

* Corresponding authors.
E-mail addresses: manojkumarpuniya114@gmail.com, manoj.kumar13@icar.gov.in (M. Kumar), Maharishi.Tomar@icar.gov.in (M. Tomar), mekhemar@konspar.uni-kiel.de (M. Mekhemar).

https://doi.org/10.1016/j.biopha.2021.112018
Received 4 July 2021; Received in revised form 30 July 2021; Accepted 7 August 2021
Available online 25 August 2021

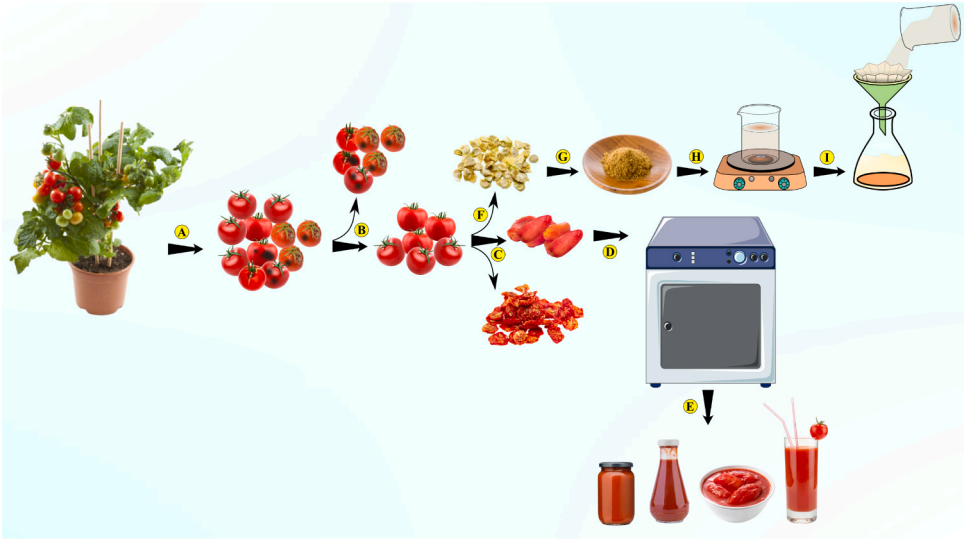
functional compounds with notable nutraceutical properties [40,116]. The arrangement of seeds in tomato fruit and the morphology of tomato seeds are shown in Fig. 1a.

After tomatoes are harvested from the plant, they are washed and sorted. Field materials are removed and the fruits are sorted manually or through electronic systems. The fruits are then peeled by using lye, steam/ or hot water. After peeling, tomatoes are again sorted and graded for final processing. These tomatoes are then used for preparing various products like jams, purees, juice and sauces. During this processing, seeds and peels are obtained as by-products. These seeds can be homogenized into a fine powder and can subsequently subjected to solvent-based extraction from making tomato seed extract (TSE) (Fig. 1b).

Tomato processing results in the production of tomato pomace, of which 60% is seed and 40% is peel [113]. The nutritional composition of tomato seeds includes proteins (32%), followed by total fat (27%) and fiber (18%). Due to their high protein content, tomato seeds have been used as a supplement in animal feeding and as a replacement in bakery products [43,74]. Owing to their thermal stability and antioxidant properties, tomato seed oil and TSEs may be utilized in food preservation [120,132]. The generation of biofuels and the production of enzymes and bioactive compounds are some of the practical applications of tomato waste [47] along with the production of tomato seed oil.

Tomato seeds are loaded with phytochemical compounds, such as gallic acid, trans-cinnamic acid and quercetin [4]. A high amount of total phenolic compounds, total flavonoids and enhanced antioxidant activity could be obtained using ethanolic extract instead of polar solvents such as water since water-soluble compounds present in tomato by-products could interfere with phenolic compounds and thereby affect their extraction efficiency [144]. In terms of lycopene extraction, the highest extraction yield is obtained using hexane [127]. A small dose of approximately 500 ppm tomato by-product extract was found to be

(a)



(b)

Fig. 1. (a) Tomato and its seeds. (b) Tomato fruit processing; (A) Fruit harvest; (B) sorting and gradation; (C) peeling of fruits and drying; (D) sterilization, and treatment of the fruit; (E) development of products; (F) removal of tomato seeds from the pulp; (G) seed homogenization into fine powder; (H and I) preparation of tomato seed extract (TSE) using specific solvents.

sufficient for controlling lipid peroxidation and could promote oil stability [4]. Tomato seeds also contain unsaponifiable compounds, including α- and γ-tocopherols and demethylsterols. Among the different demethylsterols present in tomato seeds, Δ-5-avenasterol and citrostadienol demonstrate high antioxidant activity owing to the ethyliden group at positions 24 and 28 of the side chain together with the tocopherols [52]. Approximately 17–18% of tomato seed oil is obtained by pressing dry tomato seeds, whereas it is approximately 20–23% if an extraction solvent is used [49].

This review highlights the beneficial aspects of tomato seeds in terms of human health which is attributable to their superior phytochemical profile. A comprehensive discussion of tomato seeds and their extract in various biomedical activities is well discussed along with illustrative representation.

2. Bioactives from tomato seeds

A huge amount of waste is produced during the processing of tomatoes; therefore, its utilization becomes difficult and poses a significant threat to the environment. Although some of the waste is utilized as animal feed, there is a need for further exploitation of tomato waste, including both peels and seeds.

Tomato waste is rich in bioactive components such as ß-carotene and lycopene, which have been shown to exhibit strong antioxidant activity in many studies [128]. Tomato seeds are considered a potential natural source of antioxidants because of their rich phytochemical profile. They are a reservoir of bioactive phenolic compounds (PCs) and carotenoids that play a crucial role in managing various metabolic and physiological processes in the body. Particularly, PCs (flavonoids, phenolic acids), carotenoids (β-carotene, lycopene) and nucleosides (guanidine, inosine, adenosine) are present in tomato seeds [18]. Similarly, tomato skin and pulp also contains good amount of bioactive components including flavonoids, phenolic acids, lycopene, β-carotene etc (Table 1).

Among these components, PCs exhibit several bioactivities, such as anticancer, antimicrobial, antimutagenic, anti-inflammatory, anti-neurodegeneration, antiplatelet, and cardioprotective properties. They effectively execute these activities independently or in association with other components present in tomato seeds. PCs showed promising protective mechanisms by modulating various cellular signal transduction pathways and by triggering endogenous defense activities. Dietary phytochemicals and their bioactivity epitomize their potential as functional food and pharmaceutical ingredients [98]. The phytochemical profile of tomato seeds is depicted in Table 2, and the structures of various bioactive compounds are shown in Fig. 2.

PCs, including flavonoids, are a group of small bioactive molecules characterized by a common chemical structure containing at least one aromatic ring with one or more hydroxyl moieties. PCs can modulate the sensory attributes of foods by changing flavor, taste, color, and astringency. PCs reported in foods are mostly phenolic acids and flavonoids. The phytochemical investigation of aqueous tomato seed extract led to the identification of fourteen flavonoids (13 first reported in tomato seeds), viz. quercetin, isorhamnetin, and kaempferol derivatives. A total PC content of 20,657 mg/100 g was quantified in the tomato seed extract [32]. Isorhamnetin-3-O-sophoroside plus kaempferol-3-O-sophoroside and quercetin-3-O-sophoroside were present in the highest concentrations, accounting for 59.1% and 29.2% of the total PCs, respectively. Quercetin derivatives contributed approximately 37% of the total flavonoid content. PCs such as quercetin-3-*O*-sophoroside-7-*O*-glucoside, quercetin-3-*O*-sophoroside-7-*O*-rhamnoside, kaempferol-3-sophoroside-7-*O*-glucoside, kaempferol-3-*O*-sophoroside-7-*O*--rhamnoside, quercetin-3-*O*-gentiobioside-7-*O*-glucoside, isorhamnetin-3-*O*-sophoroside-7-*O*-rhamnoside, quercetin-3-*O*-sophoroside, kaempferol-3-*O*-glucosyl-(1→2‴)-glucosyl-(1→2″)-glucoside or kaempferol-3-*O*-(2-sophorosyl)glucoside, quercetin-3-*O*-(2-pentosyl, 6-rhamnosyl)glucoside or quercetin-3-*O*-(2-pentosyl)rutinoside, isorhamnetin-3-*O*-sophoroside, kaempferol-3-*O*-sophoroside, kaempferol-3-*O*-(2-pentosyl)glucoside, and isorhamnetin-3-*O*-gentiobioside were identified for the first time in tomato seeds using high-performance liquid chromatography/photodiode array detector/electrospray ionization-mass spectrometry (HPLC/UV-PAD/MS^n-ESI) [32]. While, the essential phenolic acids in peel fraction of tomato are vanillic acid, caffeic acid, gallic acid and catechin [27]. Similarly, another studies [92] observed that tomato peel contains various flavonoids with beneficial role in human health such as naringenin and rutin. Pellicanò et al. [102] found naringenin (84.04 mg/kg DW) as the most abundant flavonoid identified followed by caffeic acid (26.60 mg/kg DW).

In another study, Valdez-Morales et al. [137] investigated bioactive phytochemicals and their antioxidant properties in seeds of four different tomato cultivars. The authors identified and quantified a total of 16 compounds comprising eight flavonoids and eight phenolic acids using HPLC-DAD. The PC contents in methanolic TSE of different cultivars were found to be 67.3–121.8 mg eq of GA/100 g and 438.3–682.8 mg eq of CAT/100 g of sample [137]. The contents of phenolic subgroups, flavonoids and tartaric esters were reported to be 50–69.2 mg eq of QUER/100 g and 3.2–6.3 mg eq of CA/100 g, respectively. The predominant phenolic acids in TSE were sinapic acid, ferulic acid, caffeic acid and ρ-coumaric acid, whereas chlorogenic acid, vanillic acid, trans-cinnamic acid and gallic acid were found in minor amounts. Similarly, flavonoids quercetin-3-O-β-glucoside and rutin were observed at higher concentrations relative to kaempferol, isorhamnetin, quercetin, naringenin, and myricetin [137]. The phenolic content in the peel of different field grown genotypes of tomato ranged from 10 to 40 mg catechins equivalents/100 g [44]. Toor and Savage [134] observed that the values of phenolics in the peel and pulp of New Zealand tomatoes fall in the same range. TPCs is significantly higher in the seeds and skin compared to the pulp of the tomato [33].

Twenty-one different bioactive compounds comprising 16 flavonoids (gallic acid, phloridzin, ferulic acid, phloretin, epicatechin, quercitrin, procyanidin B2, luteolin-7-O-glucoside, kaempferol-3-O-glucoside, apigenin-7-O-glucoside, coumaric acid, genistein, quercetin, rutin, kaempferol, daidzein), 3 nucleotides (adenosine, guanosine, inosine) and 2 carotenoids (lycopene, β-carotene) were detected in aqueous TSE using HPLC-MS. The results showed higher extraction yields in aqueous extracts (3.45% m/m) than in ethanolic extracts (1.44% m/m), which was probably due to the viscosity and polarity of extraction solvents [18]. The nucleotides, viz. guanosine, inosine, and adenosine, identified in TSE, also act as bioactive compounds due to their role in potent platelet antiaggregant activity [18,36].

Apart from phenolics, carotenoids are another class of bioactive compounds present in tomato seeds. Carotenoids are widely distributed pigments and among the most chemically and functionally diverse biomolecules on earth. Carotenoids possess immense antioxidant potential due to their ability to scavenge free radicals [103]. The various health benefits associated with carotenoid consumption include a reduced risk of some cancers, cardiovascular diseases, age-related macular degeneration and cataracts [85]. Qualitatively, the carotenoid composition of tomato seeds is similar to that of tomato fruit [111]. Carotenoid profiling of tomato seed oil showed the presence of β-carotene and lycopene isoforms (lycopene all *trans*, lycopene *cis* 1, lycopene *cis* 2, lycopene *cis* 3) by using HPLC. The authors also reported the highest β-carotene and lycopene contents in hexane-accelerated solvent extraction (ASE) treatment compared to supercritical CO_2 extraction and ethanol ASE [28]. The lycopene content in the seed fraction was quantified as 122.87 μg/g [98]. Concha-Meyer et al. [18] also identified β-carotene and lycopene in aqueous tomato seed extracts using UHPLC-MS. While, lycopene and β-carotene content in tomato peel reported as of 0.86 and 1.5 mg/100 g, respectively [102]. β-carotene, a precursor of vitamin A, is the second most abundant carotenoid reported in tomato seeds after lycopene [45]. Despite their high prevalence in tomato seeds, direct studies assessing the bio-absorption and bioavailability of compounds present in tomato seeds are not available in the current literature with most studies performed on whole tomatoes or

Table 1
Comparison of different bioactive compounds reported in seed, skin, and pulp of tomato.

Source	Bioactive compounds	References
Seed	Gallic acid (0.11–6.94 mg/100 g), Ferulic acid (1.67–9.08 mg/100 g), Kaempferol (< 0.001–2.01 mg/100 g), Quercetin (< 0.001–0.90 mg/100 g), Rutin (0.065–3.53 mg/100 g), Coumaric acid (2.58 mg/100 g), Phloridzin (1.35 mg/100 g), Phloretin (26.72 mg/100 g), Procyanidin B2 (76.62 mg/100 g), Apigenin-7-O-glucoside (0.196 mg/100 g), Kaempferol-3-O-glucoside (415.39 mg/100 g), Luteolin-7-O-glucoside (55.77 g/100 g), Genistein (0.196 mg/100 g), Daidzein (0.02 mg/100 g), Quercitrin (0.003 mg/100 g), Epicatechin (0.026 mg/100 g), Quercetin-3-O-sophoroside (6030 mg/100 g), Isorhamnetin-3-O-gentiobioside (738 mg/100 g), Quercetin-3-O-rutinoside (840 mg/100 g), Quercetin-3-O-β-glucoside (2.61–3.94 mg/100 g), Isorhamnetin (0.34–1.36 mg/100 g), Naringenin (0.16–0.35 mg/100 g), Myricetin (0.34–0.88 mg/100 g), Caffeic acid (0.95–2.19 mg/100 g), Vanillic acid (2.01 mg/100 g), Sinapic acid (1.82–3.56 mg/100 g), Chlorogenic acid (0.05–1.41 mg/100 g), ρ-cumaric acid (0.79–3.96 mg/100 g), Trans-cinnamic acid (0.10–3.01 mg/100 g), Lycopene cis 1 (0.058–0.134 mg/100 g), Lycopene cis 2 (0.106–0.302 mg/100 g), Lycopene cis 3 (0.785–0.943 mg/100 g), Lycopene all trans(0.750–1.207 mg/100 g), Lycopene (1.6–16.70 mg/100 g), β-Carotene (0.093–5.500 mg/100 g), Adenosine (< 0.001 μg/100 g), Inosine (42.21 μg/100 g), Guanosine (7.44 μg/100 g)	Silva et al. [98]; Toor and Savage [134]; Eller et al. [28]; Ferreres et al. [32]; Valdez-Morales et al. [137]; Gharbi et al. [45]; Concha-Meyer et al. [18]
Skin/peel	Chlorogenic der (33–141.10 mg/kg), p-Coumaric (07.38–26.58 mg/kg), p-Coumaric der (16.70–101.99 mg/kg), Quercetin (5.04–13.68 mg/kg), Rutin (107.06–410.13 mg/kg), Rutin der (36–109.75 mg/kg), Naringenin (73.52–287.62 mg/kg), lycopene (167.43 mg/kg dw) β-carotène (55.20 μg/g dw), lutein (065–1.54 mg/100 g), tocopherols (1.62 g/100 g dw), Caffeic acid-glucoside isomer (0.74 mg/100 g), Caffeic acid (0.55 mg/100 g) Syringic acid (0.547–1.122 mg/100 g), Di-Caffeoylquinic acid (0.812–1.113 mg/100 g), Tri-Caffeoylquinic acid (0.591−0.662 mg/100 g)	Gharbi et al. [45]; Navarro-González et al. [92]; Szabo et al. [130]
Pulp	Caffeoyl-hexoside (0.815 μg/g), Caffeoyl-hexoside isomers (0.037–0.184 μg/g), 4-Caffeoylquinic acid (0.16 μg/g), 5-p-Coumaroylquinic acid (0.032 μg/g), Quercetin-3-rutinoside (Rutin) (0.058 μg/g), Synapoyl derivative (0.093 μg/g), Caffeic acid derivative (0.105 μg/g), Lycopene (31.49 mg/100 g DW), β-carotene (10.77–21.46 mg/100 g DW)	Belović et al. [6]; Oboulbiga et al. [97]

their individual bioactive compounds (using analytical standards). For instance, a study evaluated the presence of β-carotene and lycopene in human serum and tissues and reported that the major carotenoid in the liver, adrenal gland, kidney, ovary, and fat was- β-carotene whereas lycopene was found to be the predominant carotenoid in testes [126]. Another study showed elevated levels of lycopene, phytofluene, and phytoene in human serum and protection against UV-light-induced erythema after ingestion with tomato-based products with about 10 mg/day of lycopene [3]. Different molecular mechanisms including simple diffusion and receptor-mediated transport (scavenger receptor class B type I; to transport β-carotene, lutein, and vitamin E) have been highlighted for the absorption of carotenoids by the intestinal epithelial cells [142]. Quercetin-3-O-sophoroside, a major flavonoid found in tomato seeds (Table 2), was reported to be absorbed intact, methylated and sulfated at the jejunum without deglycosylation in *in situ* rat gut model [141]. In addition, the authors also found that

Table 2
Bioactive compounds of tomato seeds.

Group	Composition	References
Phenolic compounds		
Gallic acid	0.11–6.94 mg/100 g	Concha-Meyer et al. [18] and Valdez-Morales et al. [137]
Ferulic acid	1.67–9.08 mg/100 g	
Kaempferol	< 0.001–2.01 mg/100 g	
Quercetin	< 0.001–0.90 mg/100 g	
Rutin	0.065–3.53 mg/100 g	
Coumaric acid	2.58 mg/100 g	Concha-Meyer et al. [18]
Phloridzin	1.35 mg/100 g	
Phloretin	26.72 mg/100 g	
Procyanidin B2	76.62 mg/100 g	
Apigenin-7-O-glucoside	0.196 mg/100 g	
Kaempferol-3-O-glucoside	415.39 mg/100 g	
Luteolin-7-O-glucoside	55.77 mg/100 g	
Genistein	0.196 mg/100 g	
Daidzein	0.02 mg/100 g	
Quercitrin	0.003 mg/100 g	
Epicatechin	0.026 mg/100 g	
Quercetin-3-*O*-sophoroside	6030 mg/100 g	Ferreres et al. [32]
Isorhamnetin-3-*O*-gentiobioside	738 mg/100 g	
Quercetin-3-*O*-rutinoside	840 mg/100 g	
Quercetin-3-*O*-β-glucoside	2.61–3.94 mg/100 g	Valdez-Morales et al. [137]
Isorhamnetin	0.34–1.36 mg/100 g	
Naringenin	0.16–0.35 mg/100 g	
Myricetin	0.34–0.88 mg/100 g	
Caffeic acid	0.95–2.19 mg/100 g	
Vanilic acid	2.01 mg/100 g	
Sinapic acid	1.82–3.56 mg/100 g	
Chlorogenic acid	0.05–1.41 mg/100 g	
ρ-cumaric acid	0.79–3.96 mg/100 g	
Trans-cinnamic acid	0.10–3.01 mg/100 g	
Carotenoids		
Lycopene cis 1	0.058–0.134 mg/100 g	Eller et al. [28]
Lycopene cis 2	0.106–0.302 mg/100 g	
Lycopene cis 3	0.785–0.943 mg/100 g	
Lycopene all trans	0.750–1.207 mg/100 g	
Lycopene	1.6–16.70 mg/100 g	Gharbi et al. [45]; Silva et al. [98] and Toor and Savage [134];
β-Carotene	0.093–5.500 mg/100 g	Concha-Meyer et al. [18]; Eller et al. [28] and Gharbi et al. [45]
Nucleosides		
Adenosine	< 0.001 μg/100 g	Concha-Meyer et al. [18]
Inosine	42.21 μg/100 g	
Guanosine	7.44 μg/100 g	

quercetin-3-O-sophoroside was catabolized to 11 phenolic acids by cecal microbiota [141]. The compounds and nutrients discussed in this section were tested and found to have various biological properties, which are discussed in the following Section.

3. Potential biomedical applications of tomato seed extract (TSE)

Tomato is among the most cultivated vegetables worldwide. According to FAOSTAT (http://www.fao.org/faostat/es/#data/QC), global tomato production was 182 million tons in 2018. Tomato is not only consumed fresh but also processed into cans, purees, sauces, etc. This processing releases large quantities (~1.5–5%) of by-products such as pulp, peels and seeds. These products are identified as sources of nutraceutical and bioactive compounds [78]. Seed composition is markedly different from the other fractions, as it is primarily composed of oil and protein. Seeds also contain lycopene, phenols and other compounds but in much lower amounts than the peel fractions [74]. A comprehensive snapshot of biological activities of TSE in biomedical field is presented in Table 3 and Figs. 3–6.

3.1. Anti-platelet activity/cardioprotective effect

Cardiovascular diseases (CVDs) are currently among the main causes of morbidity and mortality. Several risk factors contribute to the development of these diseases, such as obesity and high harmful cholesterol levels, hypertension or platelet activation and aggregation [2]. Tomato consumption has been correlated with cardioprotective effects [100]. Antiplatelet aggregation activity plays a key role in the prevention of atherosclerosis [36]. With respect to atherosclerosis, platelets adhere to the endothelial cell lining and help recruit leukocytes that determine local vascular inflammation. Platelets also amplify inflammation during atherosclerosis by inducing the expression of membrane-related proteins such as CD40 ligand, P-selectin and intercellular adhesion molecule-2. Additionally, platelets adhere, aggregate and secrete their constituents at the damaged atheromatous plaque. This can lead to a permanent or intermittent obstruction of blood flow causing organ dysfunction and ischemic injury. Studies have indicated that the antithrombotic activity of tomato is more often related to the whole fruit, including pulp and skin fractions, rather than only seeds [7,24,110]. Palomo et al. [99] studied the effect of tomato pomace extracts, including seeds, on platelet aggregation. The authors indicated that repeated intake of 1.0 g of tomato pomace extracts daily for 5 days significantly decreased platelet aggregation and the risk of cardiovascular diseases in human subjects. Nucleosides (guanosine, inosine and adenosine) were shown to exhibit potent activities against collagen and ADP-mediated platelet aggregation. These compounds exert their antiplatelet activities by activating cAMP/PKA-mediated signaling pathways, while the flavonoid derivatives and phenolic conjugates present in tomato seeds showed higher antiplatelet activities in response to arachidonic acid- and thrombin-mediated platelet aggregation. Certain specific flavonoids (coumaric acid, floridzin, floretin, procyanidin B2, luteolin-7-*O*-glucoside, kaempferol, and quercetin) also contributed to the anti-platelet activities. Compounds such as chlorogenic, caffeic, ferulic and p-coumaric acids present in tomato seeds may also exert similar effects [36]. The fat content of tomato seeds ranges from 15% to 30%, with 80% unsaturated fatty acids such as palmitic, oleic and linoleic acids. These fatty acids have been shown to block human platelet phospholipase A2, inhibiting atherogenesis [136]. Linoleic acid has also been shown to inhibit the development of arterial thrombosis, the expression of tissue factors, and subsequent platelet aggregation. Additionally, α-tocopherols present in seeds block platelet aggregation by a protein kinase C-mediated mechanism, explaining the reduction in P-selectin expression and interactions with platelet mononuclear cells and reducing thrombi development during stroke [37]. One recent study [18] assessed the anti-aggregating activity and chemical profile of ultrasound-assisted extracts of various tomato pomace fractions obtained through ethanol/water (1:1). The chief constituents of these extracts included coumaric acid, guanosine, inosine, kaempferol-3-*O*-glucoside, lycopene, luteolin-7-*O*-glucoside, phloretin, procyanidin B2, and quercetin, which determined the anti-platelet activities. These active extracts decreased the ADP-induced platelet aggregation from 87 ± 6% in the control to values between 26 ± 6% and 34 ± 2% at $p < 0.05$. Tomatoes also demonstrate cardioprotective roles by alleviating hyperlipidaemia and regulating gut microbiota through their seed oil. He et al. [55] demonstrated the alleviation of hyperlipidaemia in mice supplemented with tomato seed oil diets. CPT1A (carnitine palmitoyltransferase I), ACADL (acyl-CoA dehydrogenase long chain) and peroxisome proliferator-activated receptor alpha

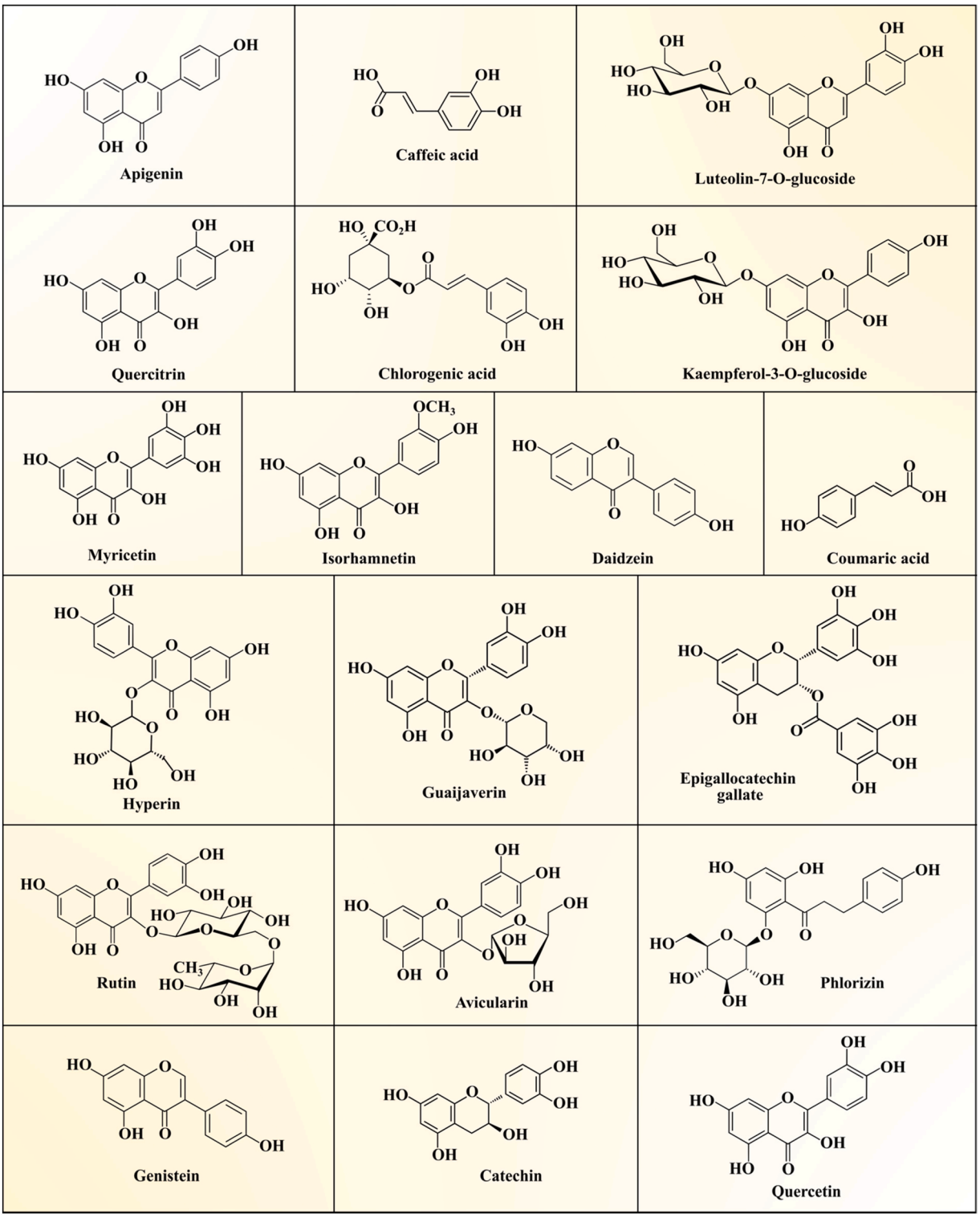


Fig. 2. Structures of different bioactive compounds in tomato seeds.

(PPAR-α) chiefly determine the β-oxidation pathway. Tomato seed oil was found to enhance β-oxidation by increasing the expression of CPT1A, ACADL and PPAR-α, subsequently reducing plasma lipid levels. The effect of TSE on the absorption of dietary fats is illustrated in Fig. 3a. Phytosterols present in tomato seed oil also suppressed cholesterol absorption due to their structural similarity with cholesterol. Tomato seed oil reduces cholesterol levels by indirectly modulating the activity of HMG-CoA reductase through sterol regulatory element-binding protein-2 (SREBP-2). The oil extracts also regulate cholesterol levels by controlling the transcription of LDLR (low-density lipoprotein receptors) through SREBP-2. A tentative model for sterol regulation through TSE is illustrated in Fig. 3b. Figure shows sterol regulatory element-binding protein cleavage-activating protein (SCAP), which is a sterol sensor and escorts sterol regulatory element-binding proteins (SREBPs). In

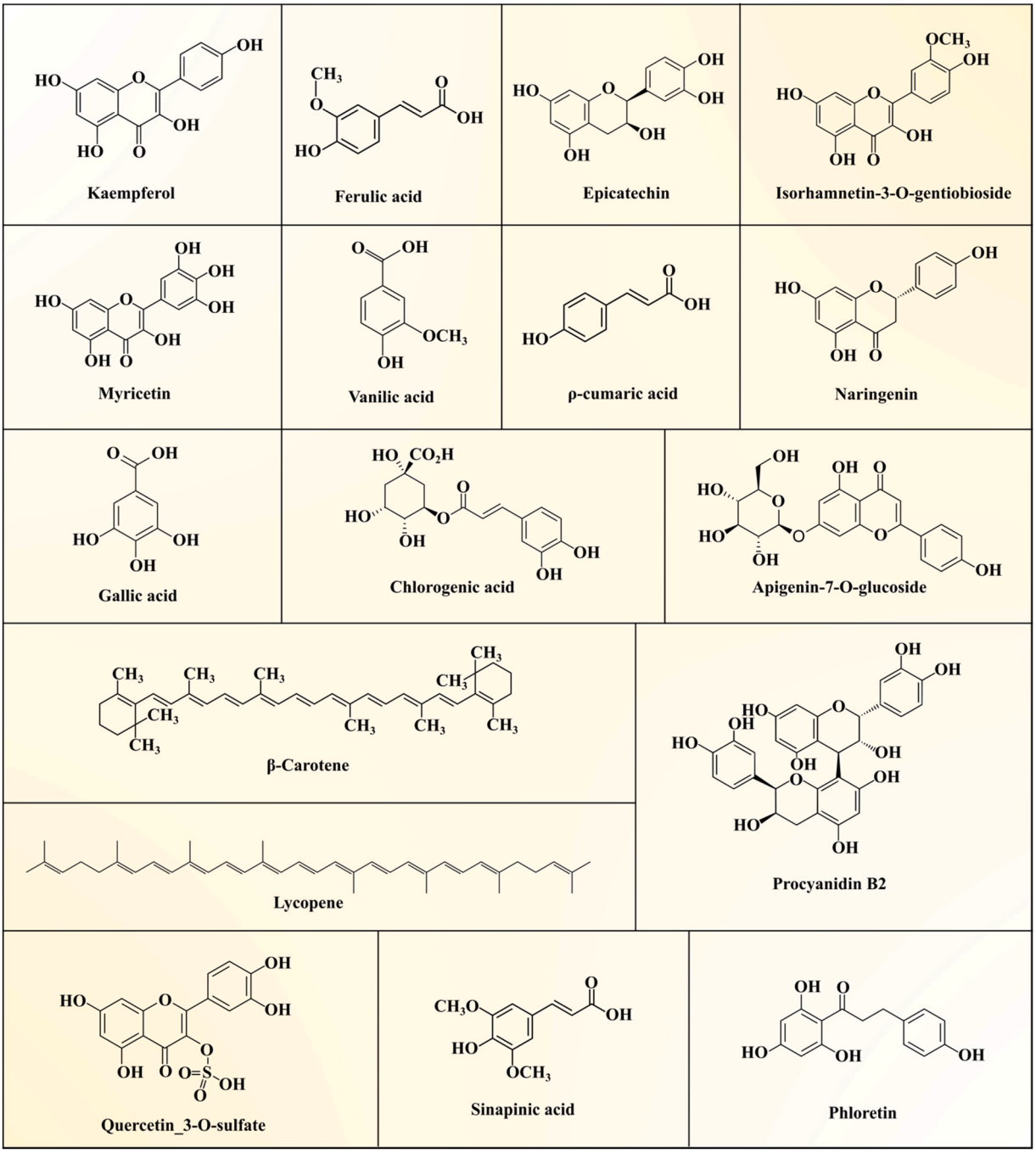


Fig. 2. (*continued*).

sterol-depleted cells, SCAP facilitates SREBP export from the endoplasmic reticulum (ER) to the Golgi apparatus. The binding of the Insig protein occludes a cytosolic binding site in SCAP. This incorporates cargo molecules (SREBPs) into vesicles, delivering ER proteins to Golgi bodies. TSE regulate cholesterol levels through SREBP-2. In the Golgi lumen, site-1 protease (S1P) and site-2 protease (S2P) act sequentially to release the transcriptionally active, N-terminal portion of the bHLH (basic helix–loop–helix)–Zip domain of SREBPs from the membrane. The released bHLH–Zip domain then further moves to the nucleus, and the bHLH–Zip domain binds a sterol response element (SRE) at the promoter/enhancer region of genes related to cholesterol and lipid biosynthesis, regulation, and transport.

Tomato seed proteins also display antihypertensive activities in the form of their bioactive sequences. Hypertension, the main cause of CVDs, is primarily regulated through the renin-angiotensin system. Angiotensin-1 converting enzyme (ACE) helps to maintain electrolytic homeostasis and mediates the conversion of angiotensin-1 (vasodilator) to angiotensin-2 (vasoconstrictor). Therefore, compounds that block ACE activity have been found to effectively control hypertension and prevent CVDs. Moayedi et al. [87] used *Bacillus subtilis* to obtain bioactive tomato seed protein hydrolysates that exhibit ACE inhibitory activity. Tomato seed protein fractions containing hydrophobic amino acids such as tryptophan, phenylalanine, tyrosine, alanine, valine, and leucine and positively charged residues such as lysine and arginine can competitively inhibit ACE activities by binding to their catalytic sites. Moreover, the ACE inhibitory activity of tomato seed meal increased 10-fold after fermentation through *Lactobacillus* spp. [78]. Therefore, further studies are necessary to differentiate the role of tomato seeds and

Table 3
Biomedical application of the tomato seed extracts in human health.

Variety	Type of extract	Bioactive compounds identified	Type of cell lines/type of study	Major findings and molecular mechanisms of action	References
Anticancer activity					
Lycopersicon esculentum Mill. 'Bull's Heart' cultivar	Tomato seed: Water/methanol (1:1) by sonication	Quercetin-3-O-sophoroside, kaempferol-3-O-sophoroside, and isorhamnetin-3-O-sophoroside	Rat basophile leukemia (RBL-2H3) cell line	A significant cell proliferation inhibition of > 80% was observed at the highest tested concentration (8 mg/mL) with an IC_{50} value of 5980 μg/mL. The molecular mechanism of action was not reported.	Ferreres et al. [32]
Black Tomato, Corbarino, San Marzano Rosso, San Marzano Giallo, San Marzano/Black Tomato hybrid and Giallo Tondo	Tomato seed: Chloroform and methanol	–	A375 malignant melanoma cells, A549 adenocarcinoma human alveolar basal epithelial cells, and HeLa cervical cancer cells	The IC_{50} values > 100 μg/mL were observed for the chloroform extracts of San Marzano/Black Tomato hybrid, San Marzano Giallo and San Marzano Rosso e Corbarino against the A375, A549 and HeLa cells. Methanolic extracts did not display any activity against the tested cell lines. The molecular mechanism of action was not reported.	Tommonaro et al. [133]
Bačka, Knjaz, Novosadski niski, O2, Rutgers and Saint Pierre	Tomato waste containing peel and seed: Ethanol extract with hexane pre-treatment	Phenolic acids (caffeic, chlorogenic, p-coumaric, ferulic and rosmarinic acid), flavonols (quercetin and rutin) and flavanone (naringenin-derivative	HeLa cervical cancer, MCF7 breast cancer and MRC-5 lung fibroblast normal cell lines	Antiproliferative effects were observed only at higher concentrations (≥ 6.3 mg/mL) in the Sulforhodamine B (SRB) assay. Saint Pierre extract exhibited the strongest antiproliferative effect against the HeLa cell line with an IC_{50} value of 13.7 mg/mL. IC_{50} values in the range 11.9–23.7 mg/mL were observed against the normal MRC-5 cells and the cancerous HeLa and MCF7 cells. In comparison, the standard compound chlorogenic acid displayed IC_{50} values of 0.49, 0.19 and > 0.50 against HeLa, MCF7 and MRC-5 cell lines, respectively. The molecular mechanism of action was not reported.	Ćetković et al. [12]
Antimutagenic activity					
Saladette, bola, grape, and cherry	Methanol	Phenolic acids (caffeic acid, ferulic acid, sinapic acid, chlorogenic acid, p-coumaric acid, trans-cinnamic acid, gallic acid, vanillic acid) and flavonoids (quercetin-3-O-βglucoside, rutin, isorhamnetin, kaempferol, naringenin quercetin, apigenin and myricetin)	*Salmonella typhimurium* YG1024	Mutagenic inhibition in the range of 40–60% was observed using 20 mg/mL of the extracts in the *S. typhimurium* assay. The molecular mechanism of action was not reported.	Valdez-Morales et al. [137]
Metabolic syndrome (MeS): Hypertension, hypercholesterolemia, diabetes-induced testicular injuries, inflammation					
Hypertension					
	Bioactive peptides generated via fermentation of tomato seed proteins with *Bacillus subtilis* A14h	Peptides with molecular mass 500–800 Da	*In vitro*	Inhibited angiotensin-1 converting enzyme (ACE) with an IC_{50} value of 1.5 mg/mL	Moayedi et al. [87]
	Bioactive peptides generated via fermentation of tomato seed proteins with *Bacillus subtilis* A14h	Hexapeptides DGVVYY, PGVPWP, VPPLYPN, PGLPKK and GYFPPP with molecular mass < 1000 Da	*In vitro*	DGVVYY, PGVPWP, VPPLYPN, PGLPKK and GYFPPP inhibited ACE-1 with the IC_{50} values of 2 μM, 19, 21 and 32 μM, respectively	Moayedi et al. [88]
	Tomato seed meal (TSM), tomato seed meal defatted (TSMD), and tomato seed meal defatted and fermented by *Lactobacillus* sp. (TSMDF)	–	*In vitro* *In-silico*	TSMDF exhibited the highest ACE inhibition with an IC_{50} value of 73.6 μg/mL) which was 10 times higher than TSMD. TSM showed weak ACE inhibition. The *in-silico* study suggested that the higher ACE inhibition activity could be attributed to vicilin (PDB6L4M) and amino aldehyde dehydrogenase (PDB4I8Q) proteins.	Maldonado-Torres et al. [78]
	Tomato seed protein hydrolysates (TSPH)		*In vitro*	Inhibited ACE with an IC_{50} value of 376 μg/mL.	Meshginfar et al. [84]
Hypercholesterolemia					
		–	*In vivo*		

(*continued on next page*)

Table 3 (*continued*)

Variety	Type of extract	Bioactive compounds identified	Type of cell lines/type of study	Major findings and molecular mechanisms of action	References
	Tomato seed oil (TSO) and defatted tomato seed (DTS)			10% TSO and 18% DTS reduced the hepatic total cholesterol content in male Golden Syrian hamsters. Protein, dietary fiber or phenolic compounds in DTS may be responsible for:	Shao et al. [119]
↓ plasma total cholesterol and low-density lipoprotein cholesterol ↑ fecal excretion of lipid, bile acid and cholesterol. ↑ hepatic CYP7A1, CYP51, ABCB11, and ABCG5					
	Tomato seed oil	–	*In vivo*	A high-dose TSO (11.8%) diet reduced the cholesterol level in C57BL/6J mice. The lipid-lowering effect of TSO supplementation is likely mediated by: ↑ fatty acid β-oxidation, ↓ cholesterol absorption, ↑ cholesterol efflux, and favorable modulation of the gut microbiota. This study demonstrated that the lipid-lowering effect of TSO is associated with gut microbiota. ↑ expression of hepatic PPARα, ACADL, CYP7A1, LXRα, ABCA1, and SR-B1.	He et al. [55]
Diabetes					
	Tomato seed	Tomatoside A	*In vitro*	Treatment of 10 μM tomatoside A for 3 h resulted in a 46.0% reduction in intestinal glucose transport in human intestinal Caco-2 cells as compared to untreated cells. ↓ GLUT2 expression via PKC signaling pathway during the ASBT-influx/MRP2-efflux process in Caco-2 cells.	Li et al. [69]
Diabetes-induced testicular injuries					
	Tomato seed essential oil	11 chemical compounds with 9,12-octadecadienoic acid (*Z,Z*)-, methyl ester, and 9-octadecenoic acid (*Z*)-, methyl ester and hexadecanoic acid, methyl ester being most abundant	*In vivo*	At higher doses of 90 and 270 mg/kg, improvements in structural changes of the testis, restoration of antioxidant defense (↑ superoxide dismutase, ↑ glutathione peroxidase and ↓ malondialdehyde activity) and testosterone levels in testicular tissue and prevention of apoptosis through upregulation the of Bcl-2 protein expression were observed in adult male rats with streptozotocin-induced diabetes	Kermani et al. [64]
Radioprotective activity					
	Tomato seed oil	Lycopene, *β*-carotene, lutein, and tocopherols	*In vivo*	An oral dose of TSO (1 mL/kg; 3 times/week for 8 weeks) before exposure to gamma radiation protected rats against ionizing radiation effect by: ↓ oxidative stress, restored lipid homeostasis, and ↓ systemic inflammation.	Ezz et al. [30]
Inflammation					
	Tomato seed oil	(5Z)-, (9Z)-, (13Z)-, and (15Z)-lycopene isomers, β-carotene, lutein, γ-tocopherol, and α-tocopherol	*In vitro*	Reduced spontaneous and H_2O_2-induced oxidative stress in THP-1 human macrophages by: ↓ phosphorylation of the MAPK ERK1/2, JNK, and p-38, activation of the redox-sensitive NF-kB, and expression of the heat shock proteins 70 and 90. ↓ ROS production	Müller et al. [91]
Antimicrobial and antifungal activity					
	Tomato seed oil	87 constituents with cycloeucalenol, oleic acid, linoleic acid, palmitic acid, and	*In vitro*	In the Hydroxyl radical scavenging activity test, TSO (EC_{50} = 2.76 ± 0.16 μg/mL) showed better antioxidant activity than that of BHT	Ma et al. (2013)

(*continued on next page*)

Table 3 (*continued*)

Variety	Type of extract	Bioactive compounds identified	Type of cell lines/type of study	Major findings and molecular mechanisms of action	References
		octadecanoic acid being major components		(EC_{50} = 436.70 ± 0.02 μg/mL). In DPPH assay, the TSO (IC_{50} = 1590.01 ± 0.01 μg/mL) exhibited relatively weaker antioxidant activity than that of BHT (IC_{50} = 69.01 ± 0.02 μg/mL). TSO showed moderate to potent, broad-spectrum antimicrobial activities against seven clinically significant bacterial strains.	
	Tomato seed	Proteins hydrolysate	*In vitro*	Hydrolysates exhibited DPPH scavenging activity (up to 70%), ferric ion reducing power, and inhibitory activity against E. coli (up to 29.8%) and B. cereus (up to 69.8%).	Moayedi et al. [86]
	Tomato seed	Quercetin-3-O-sophoroside; quercetin-3-O-rutinoside; kaempferol-3-O-(2-sophorosyl) glucoside; kaempferol-3-O-(2-pentosyl)glucoside; quercetin-3-O-(2-pentosyl)rutinoside; isorhamnetin-3-O-gentiobioside; kaempferol-3-O-sophoroside; isorhamnetin-3-O-sophoroside; aconitic acid; citric acid; malic acid; pyruvic acid; fumaric acid; acetic acid; oxalic acid; palmitoleic acid; palmitic acid; heptadecanoic acid; linoleic acid; oleic acid; stearic acid	*In vitro*	The different TSEs showed significant antibacterial activity against five Gram-positive bacteria, E. faecalis being the most susceptible one (MIC: 2.5–10 mg/mL). also, TSE showed antifungal activity against three fungi among them C. albicans was the most susceptible species (MIC: 5–10 mg/mL).	Taveira et al. [132]

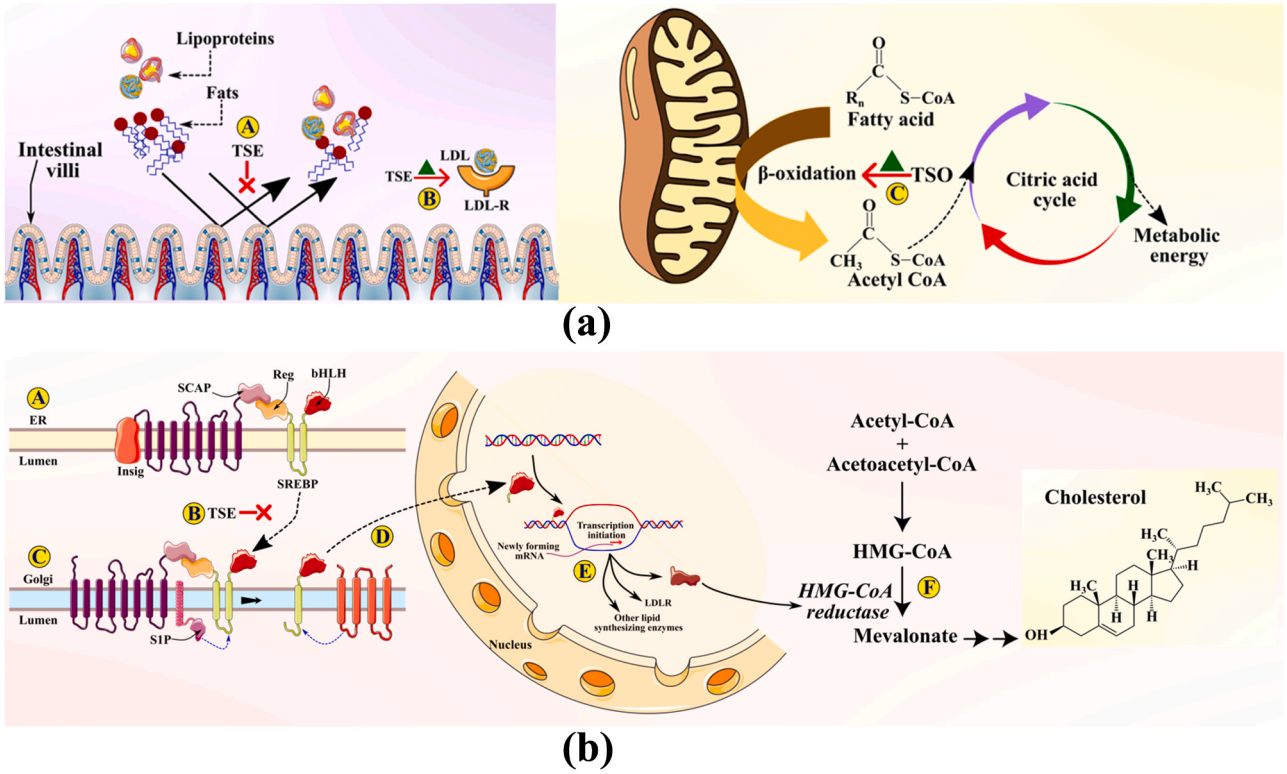


Fig. 3. (a) Effect of tomato seed extract (TSE) on the absorption of dietary fats. (A) TSE prevents the absorption of dietary fats, decreasing the plasma total cholesterol content; (B) TSE regulates the plasma fat content through LDLR (low-density lipoprotein receptors); (C) tomato seed oil (TSO) reduces the plasma level of fats by enhancing the β-oxidation pathway. (b) Tentative model for sterol regulation through tomato seed extract (TSE). (A) Sterol regulatory element-binding protein cleavage-activating protein (SCAP) is a sterol sensor that escorts sterol regulatory element-binding proteins (SREBPs). In sterol-depleted cells, SCAP facilitates SREBP export from the ER to the Golgi apparatus. The binding of the Insig protein occludes a cytosolic binding site in SCAP. This incorporates cargo molecules (SREBP) into vesicles, delivering ER proteins to the Golgi. (B) TSE regulates cholesterol levels through SREBP-2. (C) In the Golgi lumen, site-1 protease (S1P) and site-2 protease (S2P) act sequentially to release the transcriptionally active, N-terminal portion of bHLH (basic helix–loop–helix)–Zip domain of SREBPs from the membrane. (D) This released bHLH–Zip domain then further moves to the nucleus. (E) The bHLH–Zip domain binds a sterol response element (SRE) at the promoter/enhancer region of genes related to cholesterol and lipid biosynthesis, regulation, and transport. (F) Regulation and overview of cholesterol biosynthesis by HMG-CoA reductase.

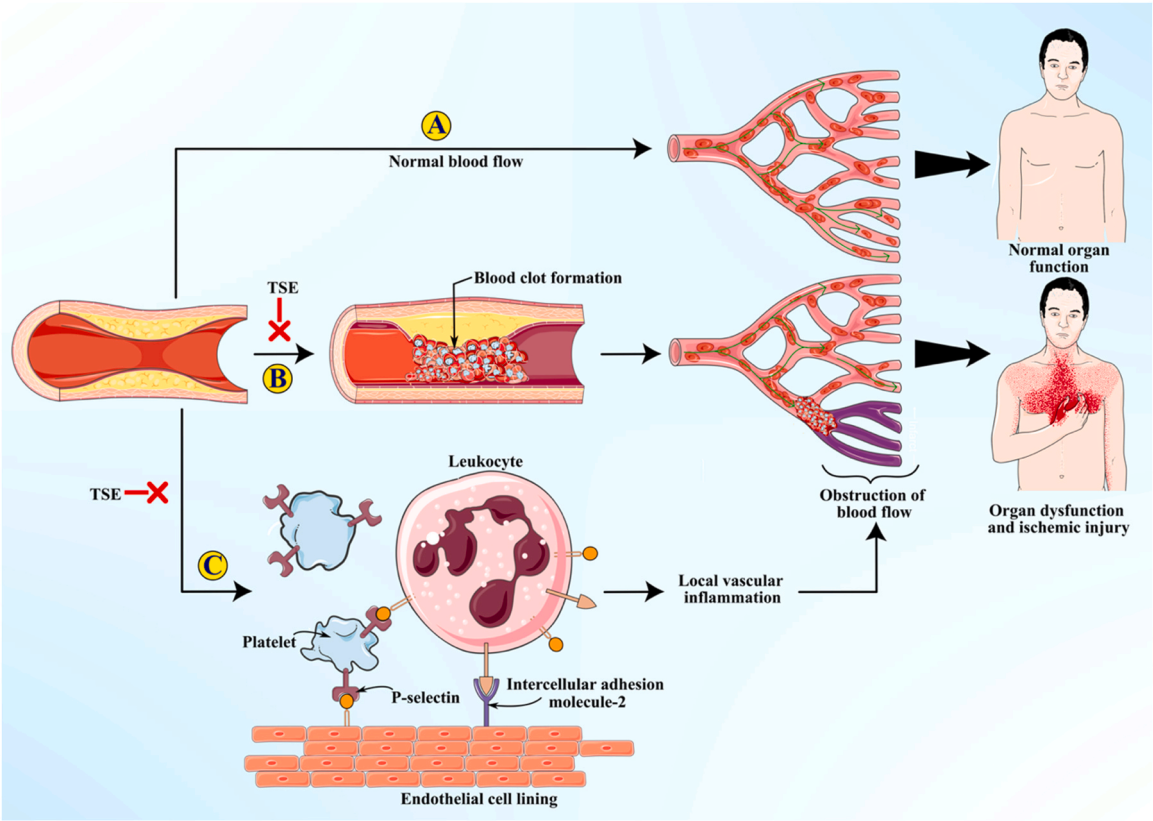


Fig. 4. Anti-platelet activity/cardioprotective effects of tomato seed extract (TSE). (A) Normal blood flow in a healthy individual; (B) prevention of blood clot formation by TSE; (C) prevention of local vascular inflammation by TSE. Platelets adhere to the endothelial cell lining by P-selectins which, in turn, recruits leukocytes through intercellular adhesion molecule-2. This subsequently results in local vascular inflammation causing permanent or intermittent obstruction of blood flow, causing organ dysfunction and ischemic injury.

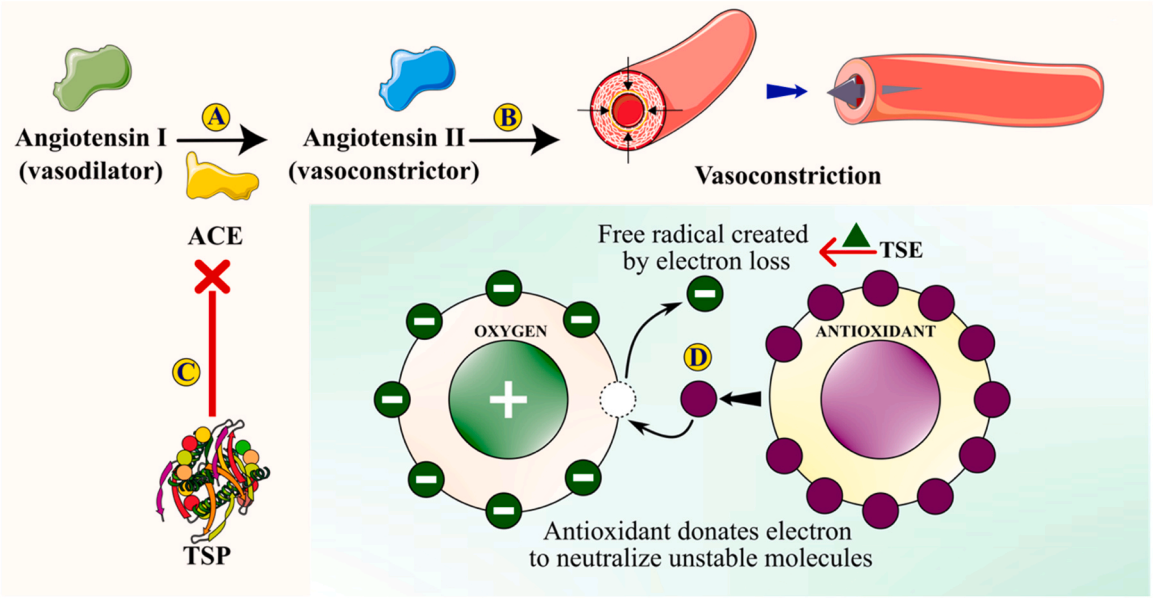


Fig. 5. Control of hypertension through the renin-angiotensin system and its regulation through TSE. (A) Angiotensin-1 converting enzyme (ACE) mediates the conversion of angiotensin-1 (vasodilator) to angiotensin-2 (vasoconstrictor); (B) vasoconstriction of blood vessels through angiotensin-2 (vasoconstrictor); (C) blockage of ACE activity by TSP (tomato seed protein) for controlling blood pressure; (D) radical scavenging and antioxidant activity of TSE.

their specific bioactive compounds in the prevention of CVDs and anti-platelet activities. Angiotensin converting enzyme 2 (ACE2) is another protein which is crucial for the entry of SARS-CoV-2 into the cell. The potential effects of TSE on ACE2 protein and its relation with SARS-CoV-2 infection is discussed in separate Section 4.

The antiplatelet activity/cardioprotective effects of TSE are depicted

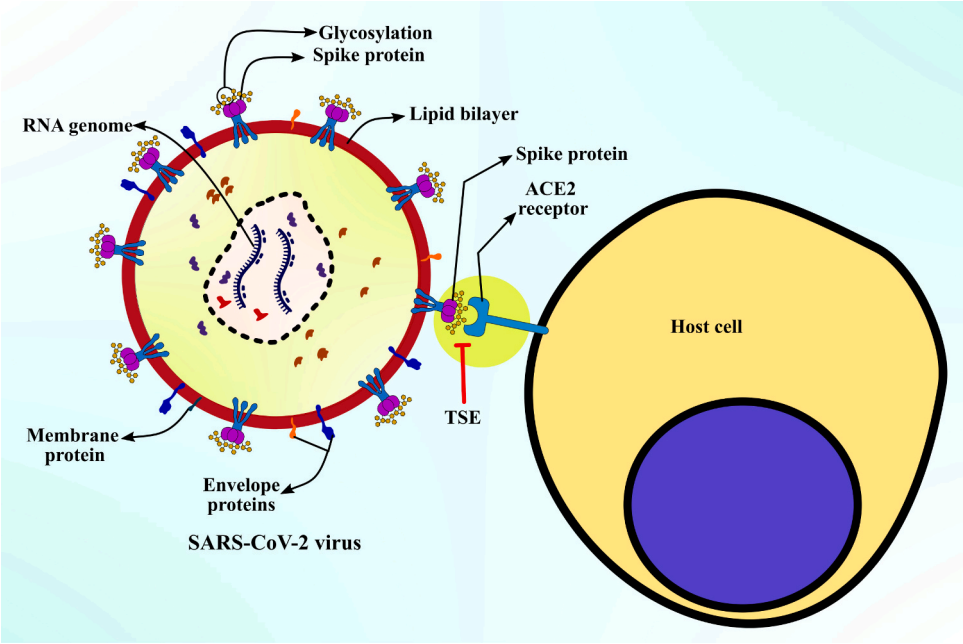


Fig. 6. Inhibition of interaction between spike glycoproteins (S-protein) and host cell surface receptors angiotensin converting enzyme 2 (ACE-2) by tomato seed extract (TSE).

in Fig. 4. This figure demonstrates the prevention of blood clot formation by TSE. During ischemic injury due to platelet aggregation, platelets adhere to the endothelial cell lining by P-selectins, which in turn recruit leukocytes through intercellular adhesion molecule-2. This subsequently results in local vascular inflammation causing permanent or intermittent obstruction of blood flow, causing organ dysfunction and ischemic injury. The prevention of this vascular inflammation by TSE is presented in Fig. 4.

3.2. *Antioxidant activity (AOA)*

There is a recent increasing consumer trend for the use of natural antioxidants in the pharmaceutical, cosmeceutical and nutraceutical industries [104]. Tomato seeds have been reported to contain antioxidant molecules such as phenols, flavonoids, condensed tannins, ascorbic acid (vitamin C), tocochromanols, and carotenoids [23,59]. Antioxidants exert their effects by interacting with free radicals that could otherwise damage vital molecules in the body [98]. These interactions include decomposition of peroxides, scavenging of radicals and binding to metal ions. Antioxidant activity is most frequently measured as radical scavenging activity in 2,2-diphenyl-1-picrylhydrazyl (DPPH), trolox equivalent antioxidant capacity (TEAC), oxygen radical absorbance capacity (ORAC), and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays, although assays investigating the reducing power of ferric iron and cupric (FRAP and CUPRAC) are common as well. Although the antioxidant activity of the whole tomato, pomace or peel has been evaluated by several authors [98,128,129], less attention has been given to the isolated seed extract. The radical scavenging and antioxidant activity of TSE is illustrated in Fig. 5.

Valdez-Morales et al. [137] determined the antioxidant activity and phenolic content of seeds and peel of tomato cultivars from Sinaloa, Mexico. These compounds primarily included caffeic acid, ferulic acid, chlorogenic acids, quercetin-3-β-*O*-glycoside, and quercetin. The peel and seeds showed higher antioxidant potential for all tested tomato varieties. Variation in antioxidant activities was also observed in tomato at different maturation stages [37]. The total antioxidant activity and phenolic content were higher in red tomato seeds than in green ripe tomato seeds. Gharbi et al. [46] stated that due to the presence of tocopherols, higher values of free radical inhibition were found in the TSEs than in other parts. The primary contributing to the antioxidant potential of TSE included lycopene, β-carotene, polyphenols and tocopherols. The total reducing power was also found to be higher in carotenoid extracts from seeds than in the peel and tocopherol extracts. Lipophilic TSEs were found to be the major contributors to the antioxidant potential. The superior radical scavenging and antioxidant activity of tomato seeds could also result from their protein fractions [118]. The bioactive compounds in tomato seed oil and phytosterols also synergistically contribute to antioxidant activities by acting as proton donors. Metal ions such as (Fe^{2+}) can instigate the production of ROS, which can harm living systems. Metal chelators can therefore inhibit ROS production and prevent damage to vital macromolecules. Tomato seed meal inherently showed lower metal chelating activity (1.1–2.2%), which was significantly enhanced (41.2%) through *Lactobacillus* spp.-based fermentation [78]. The enhancement in iron-chelating activity could result from the hydrolysis of tomato seed polysaccharides and proteins mediated by enzymes produced during fermentation. This results in the synthesis of free amino acids, bioactive peptides and hydrolysates that can effectively function as potential chelating agents. The metal chelating activities of peptide sequences containing arginine, lysine, glutamic acid, glutamine, and methionine have been thoroughly evaluated. Mechmeche et al. [82,83] fermented a tomato seed protein isolate (TSI) with different microbial strains to improve the antioxidant activity. The use of *Lactobacillus plantarum* resulted in an 87% increase in the antioxidant activity of the TSI, while the use of a water kefir microbial mixture caused a 74% increase. Similarly, the use of a *Bacillus subtilis* strain increased the radical activity of tomato seed meal (TSM) to 65% [86]. The ferric reducing power varied in a similar manner. Enzymatic hydrolysis is another common strategy to release bioactive peptides. Meshginfar, Mahoonak, Hosseinian, and Tsopmo [84] used alcalase to produce tomato seed protein hydrolysates (TSPHs). The IC_{50} value of TSPH for the DPPH assay also increased when compared to the unhydrolysed protein. In addition, linoleic acid, an omega-6 fatty acid present in tomato seeds, serves as the precursor for the synthesis of other polyunsaturated fatty acids that exhibit potent antioxidant properties [109]. Although the antioxidant potential of tomato seeds depends greatly on the variety and the state of maturation, it is comparable to that of other fractions or the whole fruit.

3.3. Anticancer and anti-mutagenic activity

As per the International Agency for Research on Cancer, World Health Organization, over 18 million cases of cancer incidence were estimated worldwide, with over 9.6 million deaths in 2018 [9]. The lack of targeted chemotherapeutic options for many cancer types and severe side effects of most chemotherapeutic drugs are some of the biggest hurdles in anticancer research. Bioactive compounds derived from natural sources have the potential to pave new avenues in cancer prevention and therapeutics.

The current literature portrays numerous reports emphasizing the preventative and therapeutic anticancer activity of tomato primarily attributed to its carotenoids (e.g., lycopene and β-carotene) and phenolic compounds [34,53,79,107,115,131] via inhibition of several signaling pathways, including interference with the IGF-I (insulin-like growth factor-1) mitogenic pathway [63]. A number of epidemiological studies have also shown that tomato consumption is associated with a lower risk of developing cancer [46,106]. Interestingly, the tomato glycoalkaloid α-tomatine, mainly found in peel [89], has also been shown to inhibit the growth of colon (HT29 and CT-26), liver (HepG2), breast (MCF-7) and gastric (AGS) cancer cell lines [34,35,65,68] via caspase-independent signaling pathways [65]. However, studies specifically investigating the anticancer properties of tomato seeds are scarce. Nevertheless, studies have indicated that tomato seeds contain several antioxidants, including lycopene, β-carotene, polyphenols and tocopherol, although in lower quantities than tomato peel seeds [46]. Parallel observations were made in another study where the removal of tomato seeds led to the reduction of 11% carotenoids, 24% phenolics and 5% antioxidant capacity [138]. The role of carotenoids, phenolic compounds, tocopherols and antioxidants from other natural sources in the prevention and treatment of cancer has been widely validated [71, 94,143]. A study found that tomato seed oil is an excellent source of linoleic acid (48.2%), palmitic acid (17.18%) and oleic acid (9.2%) [8], which have shown cytotoxicity against cancer cell lines in other studies [61]. The cytotoxic mechanism is based on the downregulation of cell death regulating factors such as Bcl-2 (B-cell lymphoma 2), which is partly regulated by elevated lipid peroxidation [15]. Additionally, these fatty acids instigate the generation of reactive oxygen species (ROS), which subsequently activate caspases and cleavage of Bid, a pro-apoptotic protein and a death agonist member of the Bcl-2 family. This further causes the release of mitochondrial cytochrome c, activating apoptosis [22]. These fatty acids also trigger the arrest of the cancer cell cycle at the G_0/G_1 phase and activation of the intrinsic apoptosis pathway So et al. [123]. In addition, these fatty acids are known to act as ligands in several signal transduction pathways and can compete in the cyclooxygenase-2 pathway for eicosanoid synthesis and enhance cellular oxidation by increased lipid peroxidation, eventually causing cancer cell death . Quercetin-3-O-sophoroside, a major flavonoid found in tomato seed (Table 2) also has been linked with potential anticancer activity [141], however, its molecular mechanisms of action and clinical efficacy against cancer have not been reported in the literature.

Table 3 shows the studies available in the literature illustrating the anticancer and antimutagenic properties of TSEs from different varieties against a number of cell lines *in vitro*. Most of these studies have reported moderate to weak activity with IC_{50} values > 100 μg/mL against different cancer cell lines [12,32,133,137]. Despite many studies indicating the antimutagenic activity of tomato extracts in *in vitro* models, such as *Salmonella typhimurium* TA98 and TA100 and V79 Chinese hamster fibroblasts [26,41,105,108], only one study by Valdez-Morales et al. [137] has reported a potential antimutagenic effect of TSEs against the *S. typhimurium* YG1024 strain (Table 3). Currently, there are no studies in the literature that demonstrate the molecular mechanisms of action by which TSEs mediate potential anticancer and antimutagenic effects. Therefore, future preclinical and clinical studies should be directed to understand the mechanistic pathways involved against cancer and to determine the potential toxicity of TSEs in cellular and animal models. Additionally, studies to isolate and identify novel anticancer compounds from tomato seeds are crucial.

3.4. Effect on metabolic syndromes

Metabolic syndrome (MeS) is an umbrella term that clusters cardiometabolic risk factors, including central obesity, dyslipidemia, insulin resistance (hyperglycemia), hypertension and other comorbidities, posing a high risk of both cardiovascular disease and type 2 diabetes [19, 21,25,114,124,145]. Other comorbidities of MeS, including a prothrombotic state, proinflammatory state, nonalcoholic fatty liver disease, and reproductive disorders, represent huge health and socioeconomic burdens in both high- and low-income countries [114, 145]. Although several preclinical and clinical studies have demonstrated the positive role of tomato and its bioactive compounds, such as phenolics and lycopene, in the management of different metabolic syndromes, such as obesity, cardiovascular diseases, diabetes and inflammation [2,107,140], reports specifically on tomato seeds are limited. Studies currently available in the literature providing direct evidence related to the potential role of tomato seed in the management of MeS are given in Table 3. Most of these reports [78,84,87,88] have suggested the inhibitory effects of tomato seeds, especially their bioactive peptides and oils, on the angiotensin-converting enzyme *in vitro,* indicating their potential antihypertensive effects (Table 3). The control of hypertension through the renin-angiotensin system and its regulation through TSE are illustrated in Fig. 5.

A study highlighted the cholesterol-lowering effects of tomato seed oil and defatted tomato seeds in the hypercholesterolemic hamster model [119]. The authors reported that the protein, viscous soluble dietary fiber (β-glucans, pectin, galactomannans) and phenolic compounds present in the defatted tomato seed could contribute to the observed hypocholesterolaemic effects in the study. Galactomannans, the main constituent of tomato seed endosperm, increased the intestinal content viscosity and impeded the enterohepatic cycle of bile acids [119]. Another study by Liu et al. [72] demonstrated that tomato seed oil can reduce the blood sugar content and improve the glucose tolerance in diabetic mice potentially by regulating the levels of MAD, SOD and GSH-PX. Diverse phenolic compounds in tomato seeds, including chlorogenic acid, naringenin, isorhamnetin, kaempferol and quercetin, exhibit anti-obesity and hypocholesterolaemic properties by regulating lipid metabolism-related hepatic gene expression [13,62]. The primary mechanism of defatted tomato seed-mediated cholesterol reduction, specifically (low-density lipoprotein cholesterol and hepatic cholesterol), relies on the fecal excretion of lipids and cholesterol [119]. Upregulation of hepatic genes such as ABCG5, ABCB11, CYP51 and CYP7A1 increases bile acid synthesis and subsequent cholesterol excretion [119]. Low-density lipoprotein receptors are also upregulated, which increases the transport of cholesterol and lipids from blood to the liver, consequently lowering the plasma cholesterol and lipid content [119].

The molecular mechanisms through which tomato seed meal, oil or peptides mediate these therapeutic effects against MeS are highly speculative due to the scarcity of preclinical and clinical studies. Interestingly, policosanol, a mixture of long-chain linear fatty alcohols (n-alkanols) found in a wide range of tomato cultivars [48], has been demonstrated to significantly reduce total cholesterol, low-density lipoprotein (LDL) cholesterol, the ratio of LDL cholesterol/high-density lipoprotein (HDL)-cholesterol, and the ratio of total cholesterol/HDL cholesterol and enhance HDL cholesterol levels compared to baseline and placebo in non-insulin-dependent diabetes mellitus patients [11, 135]. Similar effects of policosanol were also observed in older patients with hypertension and type II hypercholesterolemia [10]. In monkeys, policosanol has shown to increase apoA-1 localization in aortic atherosclerotic lesions and reduce the presence of macrophages and the occurrence of apoB in comparison to the control monkeys suggesting its

potential benefit on atherosclerosis development [95]. The potential health benefits of policosanol against MeS have been illustrated in several preclinical and clinical studies [29,67,73,96,121]. Policosanol is commercially isolated from sugarcane wax for medicinal use [11]. Given the limited evidence of tomato seed efficacy against MeS, further preclinical and clinical studies using different disease models to understand the involvement of different molecular pathways are prudent.

3.5. Anti-inflammatory activity

Studies on the anti-inflammatory activity of tomato seeds are limited. Only one *in vitro* study by Müller et al. [91] reported the involvement of MAPK, ERK1/2, JNK, p-38 protein, NF-kB and heat shock proteins 70 and 90 in mediating the anti-inflammatory effects of tomato seed oil on THP-1 human macrophage cells. A recent study Choe et al. [17] demonstrated that tomato seed flour extracts dose-dependently suppressed the mRNA expression of the pro-inflammatory markers including IL-1β, IL-6, and TNF-α (tumor necrosis factor) and identified bioactive compounds such as malic acid, 2-hydroxyadipic acid, salicylic acid, naringin, N-acetyl-tryptophan, quercetin-di-O-hexoside, kaempferol-di-O-hexoside, and azelaic acid in the tomato seed flour. Another report demonstrated the therapeutic effects of tomato seed oil on diabetes-induced testicular injuries [64]. Hyperglycemic conditions induce apoptosis in the testes of diabetic rats, accompanied by downregulation of *Bcl-2* gene expression. Tomato seed oil impedes testicular apoptosis by upregulating *Bcl-2* expression. Phenolic compounds such as quercetin, melatonin and ferulic acid also prevent the effects of post-diabetes testicular damage. It has been established that TNF-α causes insulin resistance by blocking IRS1 (insulin receptor substrate 1) and that interleukin-1β induces the apoptosis of β-pancreatic cells, decreasing insulin production. Aqueous TSEs block the expression of TNF-α and interleukin-1β by inhibiting the expression of the transcription factor NF-κB (nuclear factor kappa B), thereby preventing diabetes symptoms and testicular damage. Quercetin-3-O-sophoroside, one of the major bioactive compounds of tomato seed (Table 1) and broccoli also has been linked with anti-inflammatory activity in several studies [141].

3.6. Neuroprotection

Despite the presence of a diverse group of antioxidant compounds, the neuromodulatory effects of aqueous tomato TSE have not been extensively investigated. In a study, TSE was evaluated for its neuroprotective effect by its ability to attenuate neurotoxicity and rotenone (mitochondrial complex I blocker)-induced oxidative stress in mice [50]. The oral dose of TSE in mice offset rotenone-induced oxidative deterioration, reinstated glutathione levels and stimulated the antioxidant defense system (glutathione peroxidase, superoxide dismutase). It also lowered the activity of rotenone-induced acetylcholinesterase and revived dopamine in the striatum. Intriguingly, TSE was shown to effectively restore mitochondrial complex activities and maintain their redox state.

Researchers have indicated that oral administration of TSE exhibits a high propensity to offer neuroprotection against neurotoxicants and other neurodegenerative ailments, such as Parkinson's disease. The disease is associated with midbrain basal ganglia dopaminergic malfunctioning which result into motor impairment ultimately causing gait and neurobehavioral abnormalities. Flavonoids such as myricetin, kaempferol and quercetin present in TSE are metabolized through the intestinal microflora to produce hydroxyphenyl acetic acids that display anxiolytic effects [139]. Additionally, lycopene in TSE alleviates oxidative dysfunction of the mitochondria. The same research group also studied the neuroprotective effects of TSE on rotenone-induced neurotoxicity in *Drosophila*. TSE was found to protect flies against death, oxidative stress, neurotoxicity and locomotory defects [66].

3.7. Antimicrobial activities

The antimicrobial activities of TSE can be exploited by the pharmaceutical and food industries to preserve food and prevent microbial spoilage. Seed containing tomato processing waste was fermented using *Bacillus subtilis* culture to generate hydrolysates with potential antibacterial and antioxidant activities [86]. These hydrolysates showed strong antioxidant activities against *Bacillus cereus* and *Escherichia coli* by reducing their growth rates up to 69.8% and 29.8%, respectively [86]. The researchers indicated that the antimicrobial properties of the hydrolysate were attributed to the bioactive peptides generated during fermentation. Similarly, the phenolic and carotenoid contents of ten tomato variety processing wastes were correlated with their antimicrobial properties [128]. The extracts showed promising antimicrobial activities against gram-positive bacteria such as *Staphylococcus aureus*, with an MIC (minimum inhibitory concentration) of 0.625 mg tomato waste/mL, *B. subtilis* with an MIC of 1.25 mg tomato waste/mL, *L. monocytogenes* with an MIC of 2.50 mg tomato waste/mL and *K. pneumonia* with an MIC of 2.50 mg tomato waste/mL. The activities were directly correlated with the isochlorogenic acid content. The main compounds included lycopene, β-Carotene, lutein, carotenoids, phenolic compounds (quercetin-triglucoside, quercetin-3-rutinoside, 3,4-di-O--caffeoylquinic (isochlorogenic) acid, 3,4,5-tri-caffeoylquinic acid, naringenin chalcone and naringenin).

Taveira et al. [132] tested the antimicrobial activity of TSEs against gram-negative bacteria (*Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus mirabilis*), gram-positive bacteria (*Bacillus cereus*, *Enterococcus faecalis*, *Micrococcus luteus*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*) and fungi (*Trichophyton rubrum*, *Aspergillus fumigatus*, and *Candida albicans*). The extracts showed the highest antimicrobial activity against *E. faecalis* with an MIC of 2.5–10 mg/mL and *C. albicans* at an MIC of 5–10 mg/mL. These extracts chiefly contained phenolics [quercetin-3-*O*-(2-pentosyl) rutinoside, kaempferol-3-*O*-(2-sophorosyl) glucoside, quercetin-3-*O*-sophoroside], organic acids [oxalic, aconitic, citric, pyruvic, malic, acetic and fumaric acids] and fatty acids [pentadecanoic, palmitic, heptadecanoic, stearic, palmitoleic, oleic and linoleic acids] which determined their bioactivities. Organic acids such as fumaric acid were found to be active against all tested microbes by reducing the intracellular and environmental pH. Rutin, a flavonoid, was also found to demonstrate antimicrobial properties by its tendency to change microbial cell permeability, resulting in a loss of cellular macromolecules and ions, deformations of vital cellular proteins and inactivation of enzymes. Fatty acids show bactericidal potential due to their ability to alter cell membrane integrity through their hydrophobic and hydrophilic structural components. Although much research has been performed on the bioactivities of tomato waste, the main focus has been on pomace and peel fractions, while only a handful of reports on seeds. Tomato seeds contain several metabolites, such as fatty acids, carotenoids, phenolic compounds, proteins, amino acids and vitamins. Phenolic compounds and carotenoids are the most studied, and correlations have been found between their levels and antioxidant or antimicrobial bioactivity. Nevertheless, tomato seeds can also exert bioactivity via their oil and proteins.

4. Potential effects of TSE on ACE2 protein

Coronaviruses (CoVs) is a positive-stranded RNA virus family that cause life- threatening infections causing severe breathing disorders and severe pneumonia in human beings. Presently, three single-stranded RNA beta-coronaviruses, have been detected which include MERS (Middle East respiratory syndrome) virus, SARS (severe acute respiratory syndrome) virus and SARS-CoV-2 [51,56]. The coronavirus discovered in 2019 was designated by the World Health Organization (WHO) as SARS-CoV-2 or 2019-novel coronavirus (2019 nCoV). On February 11, 2020, WHO announced the disease caused by 2019-nCoV as Coronavirus Disease 2019 (COVID-19) [14]. The ongoing COVID-19

pandemic caused by SARS-CoV-2 is presently the highest priority research, worldwide [57]. The clinical manifestations of this disease occur after an incubation period of about 5–7 days, including lymphopenia, dyspnea, diarrhea, headache, fatigue, fever, and cough [20]. Although, most of the patients experience mild to moderate symptoms or are even asymptomatic, some may develop acute respiratory distress syndrome (ARDS), respiratory or multiple organ failure [125]. Complications caused by severe COVID-19 infections include heart failure, liver dysfunction, kidney damage, cardiac arrhythmia, metabolic acidosis, lung damage, systemic hyper-inflammation, coagulation dysfunction, septic shock, and ARDS.

The chief immunogenic constituents of coronaviruses are the spike glycoproteins (S-protein) that interacts with cell surface receptors called ACE-2, and subsequently enters the host cells [42,54,70]. ACE-2 (integral membrane protein type I), the human receptor for of SARS-CoV-2 is highly expressed on the surface of brain, endothelial, intestinal, cardiac, renal, and alveolar epithelial type II cells, which are the primary COVID-19 target organs [5]. ACE-2 is pivotal for the entry and subsequent replication of SARS-CoV-2; however, once attached, translocation and replication of virus is succeeded by the depletion of ACE-2 [1]. Since the chief role of ACE-2 is to cleave proinflammatory angiotensin II (AngII) into anti-inflammatory angiotensin1-7 (Ang1-7) [117], the binding of SARS-CoV-2, prevents the synthesis of Ang1-7, resulting in the accumulation of AngII. This is considered as the crucial mechanism in the COVID-19 induced acute lung injury.

When the cells are invaded by multiple viral particles, the entire cellular protein synthesis machinery is dedicated to vital replication. The new viral particles are then assembled and released through exocytosis, followed by the host cell death by apoptosis. The released viral copies infect other cells and organs. After the vital antigens are recognized by the immune system, the antigen-presenting cells introduce the viral antigens to CD8-positive cytotoxic T-cells and natural killer (NK) cells. This is followed by the activation of adaptive and innate immunity, resulting in the production of proinflammatory chemokines and cytokines [125]. Cytokines are secreted proteins which have a definite effect on regulation, differentiation, and development of immune cells [112].

Since the onset of COVID-19, extended attempts have been made to discover vaccine/ drug against SARS-CoV-2. The presence of diverse phytochemicals in TSE, could be used as helpful candidates for treating and preventing viral diseases like COVID-19 [31,58] Mohammadi et al. [90]. Flavonoids present in TSE can demonstrate immunomodulatory and anti-viral activities against coronaviruses [93]. These activities of TSE flavonoids could be associated with SARS-CoV-2 spike-protein and ACE-2 receptors. This was demonstrated by the molecular docking and bioinformatics in case of theaflavin gallate and epigallocatechin-3-gallate [77], kaempferol, quercetin, fisetin [101], naringenin, naringin, nobiletin, myricetin, luteolin, hesperidin, quercetin [80]. Flavonoids like caflanone, linebacker, myricetin, and hesperetin demonstrated excellent binding affinities to helicase, protease, ACE-2 receptor and S protein, blocking the viral entry [93]. Another study demonstrated that naringenin exhibited low binding energy for ACE-2 receptor, indicating a high binding affinity towards ACE-2 [16]. Similarly, [60], demonstrated the inhibition of interaction between S protein of SARS-CoV-2 and S protein by chrysin.

Furthermore, polyphenolic compounds present in TSE like coumarins, also display ACE2 modulatory activities. Both *in vitro* and *in vivo* studies indicate that coumarins mitigate acute lung injury and inflammation in mice by inhibiting the down-regulation Ang (1−7) and ACE2, resulting in lower release of proinflammatory cytokines (IL-6 and TNF-α) [122]. An illustration showing inhibition of interaction between spike glycoproteins (S-protein) and host cell surface receptors ACE-2 by TSE is shown in Fig. 6.

5. Conclusion and future perspectives

Tomato is a widely cultivated and globally in-demand commodity due to its savory flavor, rich nutrient content, and health-promoting properties. This review has shown that seed waste generated during tomato fruit processing also carries a significant amount bioactives which are ultimately responsible for immense health promoting activities. The findings of *in vitro* and *in vivo* studies with animal models along with human cell lines using TSEs justify its promising benefits, such as its use in potent antiplatelet, antioxidant, anticancer, antimutagenic, antimicrobial, and neuroprotective agents. Given this superior nutritional and nutraceutical background, tomato seeds have applicability as an active ingredient in the development of functional foods.

A multifaceted research approach has promoted the utilization of tomato seed waste as a salutary ingredient for the food industry. However, further research should be aimed at unraveling the in-depth molecular mechanism underlying the bioactivities of TSEs. More understanding of the efficacy and safety of nutraceutical compounds from TSEs for functional food and pharmacological applications is necessary. Furthermore, information on the bioavailability and bioaccessibility of several compounds from tomato seeds in the human body is scarce. Randomized clinical studies on tomato seed-based functional food products to evaluate their efficacy and safety will magnify the valorization capabilities of tomato seeds for utilization in the functional food, cosmeceutical, and pharma industries.

CRediT authorship contribution statement

Manoj Kumar: Supervision**,** Conceptualization, Software, Writing – original draft, Writing – review & editing. **Maharishi Tomar**: Conceptualization, Software, Writing – original draft, Writing – review & editing. **Deep Jyoti Bhuyan**: Conceptualization, Software, Writing – original draft, Writing – review & editing. **Sneh Punia**: Writing – original draft, Visualization. **Simona Grasso**: Writing – original draft, Visualization. **Amanda Gomes Almeida Sá**: Writing – original draft, Visualization. **Bruno Augusto Mattar Carciofi**: Writing – original draft, Visualization. **Fatima Arrutia**: Writing – original draft, Visualization. **Sushil Changan**: Writing – original draft, Visualization, Writing – review & editing. **Radha**: Writing – original draft, Visualization. **Surinder Singh**: Writing – original draft, Visualization. **Sangram Dhumal**: Writing – original draft, Visualization. **M. Senapathy**: Writing – original draft, Visualization, Writing – review & editing. **Varsha Satankar**: Writing – original draft, Visualization, Writing – review & editing. **T. Anitha**: Writing – original draft, Visualization, Writing – review & editing. **Anshu Sharma**: Writing – original draft, Visualization, Writing – review & editing. **R. Pandiselvam**: Writing – original draft, Visualization, Writing – review & editing. **Ryszard Amarowicz**: Conceptualization, Software, Writing – original draft, Writing – review & editing. **Mohamed Mekhemar**: Conceptualization, Software, Writing – original draft, Writing – review & editing.

Declaration of conflicting interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the University of Kiel and SchleswigHolstein for the support through the OA program.

References

[1] Z. Abassi, A.A.R. Higazi, S. Kinaneh, Z. Armaly, K. Skorecki, S.N. Heyman, ACE2, COVID-19 infection, inflammation, and coagulopathy: missing pieces in the puzzle, Front. Physiol. 11 (2020), 1253.

[2] P. Alam, M.A. Raka, S. Khan, J. Sarker, N. Ahmed, P.D. Nath, N. Hasan, M. M. Mohib, A. Tisha, M.A. Taher Sagor, A clinical review of the effectiveness of tomato (Solanum lycopersicum) against cardiovascular dysfunction and related metabolic syndrome, J. Herb. Med. 16 (2019), 100235, https://doi.org/10.1016/j.hermed.2018.09.006.

[3] O. Aust, W. Stahl, H. Sies, H. Tronnier, U. Heinrich, Supplementation with tomato-based products increases lycopene, phytofluene, and phytoene levels in human serum and protects against UV-light-induced erythema, Int. J. Vitam. Nutr. Res. 75 (1) (2005) 54–60.

[4] S. Azabou, H. Sebii, F. Taheur, Ben, Y. Abid, M. Jridi, M. Nasri, Phytochemical profile and antioxidant properties of tomato by-products as affected by extraction solvents and potential application in refined olive oils, Food Biosci. 36 (2020), 100664, https://doi.org/10.1016/j.fbio.2020.100664.

[5] P. Bellavite, A. Donzelli, Hesperidin and SARS-CoV-2: new light on the healthy function of citrus fruits, Antioxidants 9 (8) (2020) 742.

[6] M.M. Belović, A. Gironés-Vilaplana, D.A. Moreno, I.L. Milovanović, A. R. Novaković, M.A. Karaman, N.M. Ilić, Tomato (Solanum lycopersicum L.) processing main product (juice) and by-product (pomace) bioactivity potential measured as antioxidant activity and angiotensin-converting enzyme inhibition, J. Food Process. Preserv. 40 (6) (2016) 1229–1237.

[7] D. Biswas, M.M. Uddin, L.L. Dizdarevic, A. Jørgensen, A.K. Duttaroy, Inhibition of angiotensin-converting enzyme by aqueous extract of tomato, Eur. J. Nutr. 53 (8) (2014) 1699–1706, https://doi.org/10.1007/s00394-014-0676-1.

[8] C. Botineștean, N.G. Hădărugă, D.I. Hădărugă, I. Jianu, Fatty acids composition by gas chromatography–mass spectrometry (GC-MS) and most important physical–chemicals parameters of tomato seed oil, J. Agroaliment. Process. Technol. 18 (1) (2012) 89–94.

[9] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424, https://doi.org/10.3322/caac.21492.

[10] G. Castaño, R. Más, J.C. Fernández, L. Fernández, J. Illnait, E. López, Effects of policosanol on older patients with hypertension and type II hypercholesterolaemia, Drugs RD 3 (3) (2002) 159–172, https://doi.org/10.2165/00126839-200203030-00004.

[11] G. Castaño, R. Mas, L. Fernández, J. Illnait, R. Gámez, E. Alvarez, Effects of policosanol 20 versus 40 mg/day in the treatment of patients with type II hypercholesterolemia: a 6-month double-blind study, Int. J. Clin. Pharmacol. Res. 21 (1) (2001) 43–57.

[12] G. Ćetković, S. Savatović, J. Čanadanović-Brunet, S. Djilas, J. Vulić, A. Mandić, D. Četojević-Simin, Valorisation of phenolic composition, antioxidant and cell growth activities of tomato waste, Food Chem. 133 (3) (2012) 938–945, https://doi.org/10.1016/j.foodchem.2012.02.007.

[13] C.J. Chang, T.-F. Tzeng, S.-S. Liou, Y.-S. Chang, I.M. Liu, Kaempferol regulates the lipid-profile in high-fat diet-fed rats through an increase in hepatic PPARa levels, Planta Med. 77 (17) (2011) 1876–1882, https://doi.org/10.1055/s-0031-1279992.

[14] Y. Chen, Q. Liu, GuoD, Emerging coronaviruses: genome structure, replication, and pathogenesis, J. Med. Virol. 92 (2020) 418–423.

[15] Z.Y. Chen, N.W. Istfan, Docosahexaenoic acid is a potent inducer of apoptosis in HT-29 colon cancer cells, Prostaglandins Leukot. Essent. Fat. Acids 63 (5) (2000) 301–308, https://doi.org/10.1054/plef.2000.0218.

[16] L. Cheng, W. Zheng, M. Li, et al., Citrus fruits are rich in flavonoids for immunoregulation and potential targeting ACE2, Preprints 2020 (2020), 2020020313.

[17] U. Choe, J. Sun, E. Bailoni, P. Chen, Y. Li, B. Gao, L.L. Yu, Chemical composition of tomato seed flours, and their radical scavenging, anti-inflammatory and gut microbiota modulating properties, Molecules 26 (5) (2021) 1478.

[18] A. Concha-Meyer, I. Palomo, A. Plaza, A. Gadioli Tarone, M.R. Maróstica Junior, S.G. Sáyago-Ayerdi, E. Fuentes, Platelet anti-aggregant activity and bioactive compounds of ultrasound-assisted extracts from whole and seedless tomato pomace, Foods 9 (11) (2020), https://doi.org/10.3390/foods9111564.

[19] M.-A. Cornier, D. Dabelea, T.L. Hernandez, R.C. Lindstrom, A.J. Steig, N.R. Stob, R.E. Van Pelt, H. Wang, R.H. Eckel, The metabolic syndrome, Endocr. Rev. 29 (7) (2008) 777–822, https://doi.org/10.1210/er.2008–0024.

[20] V.J. Costela-Ruiz, R. Illescas-Montes, J.M. Puerta-Puerta, C. Ruiz, L. Melguizo-Rodríguez, SARS-CoV-2 infection: the role of cytokines in COVID-19 disease, Cytokine Growth Factor Rev. 54 (2020) 62–75.

[21] K. Dabke, G. Hendrick, S. Devkota, The gut microbiome and metabolic syndrome, J. Clin. Investig. 129 (10) (2019) 4050–4057, https://doi.org/10.1172/JCI129194.

[22] U.N. Das, From bench to the clinic: gamma-linolenic acid therapy of human gliomas, Prostaglandins Leukot. Essent. Fat. Acids 70 (2004) 539–552, https://doi.org/10.1016/j.plefa.2003.12.001.

[23] M. Durante, A. Montefusco, P.P. Marrese, M. Soccio, D. Pastore, G. Piro, G. Mita, M.S. Lenucci, Seeds of pomegranate, tomato and grapes: an underestimated source of natural bioactive molecules and antioxidants from agri-food by-products, J. Food Compos. Anal. 63 (2017) 65–72, https://doi.org/10.1016/j.jfca.2017.07.026.

[24] A.K. Dutta-Roy, L. Crosbie, M.J. Gordon, Effects of tomato extract on human platelet aggregation in vitro, Platelets 12 (4) (2001) 218–227, https://doi.org/10.1080/09537100120058757.

[25] R.H. Eckel, S.M. Grundy, P.Z. Zimmet, The metabolic syndrome, Lancet 365 (9468) (2005) 1415–1428, https://doi.org/10.1016/S0140-6736(05)66378-7.

[26] R. Edenharder, P. Kurz, K. John, S. Burgard, K. Seeger, In vitro effect of vegetable and fruit juices on the mutagenicity of 2-amino-3-methylimidazo[4,5-f]quinoline, 2-amino-3,4-dimethylimidazo[4,5-f]quinoline and 2-amino-3,8-dimethylimidazo [4,5-f]quinoxaline, Food Chem. Toxicol. 32 (5) (1994) 443–459, https://doi.org/10.1016/0278-6915(94)90042-6.

[27] E. Elbadrawy, A. Sello, Evaluation of nutritional value and antioxidant activity of tomato peel extracts, Arab. J. Chem. 9 (2016) S1010–S1018.

[28] F.J. Eller, J.K. Moser, J.A. Kenar, S.L. Taylor, Extraction and analysis of tomato seed oil, JAOCS J. Am. Oil Chem. Soc. 87 (7) (2010) 755–762, https://doi.org/10.1007/s11746-010-1563-4.

[29] M.M. Elseweidy, N. Zein, S.E. Aldhamy, M.M. Elsawy, S.A. Saeid, Policosanol as a new inhibitor candidate for vascular calcification in diabetic hyperlipidemic rats, Exp. Biol. Med. 241 (17) (2016) 1943–1949.

[30] M.K. Ezz, N.K. Ibrahim, M.M. Said, M.A. Farrag, The beneficial radioprotective effect of tomato seed oil against gamma radiation–induced damage in male rats, J. Diet. Suppl. 15 (6) (2018) 923–938, https://doi.org/10.1080/19390211.2017.1406427.

[31] S. Fakhri, Z. Nouri, S.Z. Moradi, M.H. Farzaei, Astaxanthin, COVID-19 and immune response: focus on oxidative stress, apoptosis and autophagy, Phytother. Res. (2020).

[32] F. Ferreres, M. Taveira, D.M. Pereira, P. Valentão, B. Andrade, P, Tomato (Lycopersicon esculentum) seeds: new flavonols and cytotoxic effect, J. Agric. Food Chem. 58 (5) (2010) 2854–2861, https://doi.org/10.1021/jf904015f.

[33] I.R. Flores, M.S. Vásquez-Murrieta, M.O. Franco-Hernández, C.E. Márquez-Herrera, A. Ponce-Mendoza, M. del Socorro López-Cortéz, Bioactive compounds in tomato (Solanum lycopersicum) variety saladette and their relationship with soil mineral content, Food Chem. 344 (2021), 128608.

[34] M. Friedman, Anticarcinogenic, cardioprotective, and other health benefits of tomato compounds lycopene, α-tomatine, and tomatidine in pure form and in fresh and processed tomatoes, J. Agric. Food Chem. 61 (40) (2013) 9534–9550, https://doi.org/10.1021/jf402654e.

[35] M. Friedman, C.E. Levin, S.-U. Lee, H.-J. Kim, I.-S. Lee, J.-O. Byun, N. Kozukue, Tomatine-containing green tomato extracts inhibit growth of human breast, colon, liver, and stomach cancer cells, J. Agric. Food Chem. 57 (13) (2009) 5727–5733, https://doi.org/10.1021/jf900364j.

[36] E.J. Fuentes, L.A. Astudillo, M.I. Gutiérrez, S.O. Contreras, L.O. Bustamante, P. I. Rubio, R. Moore-Carrasco, M.A. Alarcón, J.A. Fuentes, D.E. González, I. F. Palomo, Fractions of aqueous and methanolic extracts from tomato (Solanum lycopersicum L.) present platelet antiaggregant activity, Blood Coagul. Fibrinolysis 23 (2) (2012) 109–117, https://doi.org/10.1097/MBC.0b013e32834d78dd.

[37] E. Fuentes, R. Carle, L. Astudillo, L. Guzmán, M. Gutiérrez, G. Carrasco, I. Palomo, Antioxidant and antiplatelet activities in extracts from green and fully ripe tomato fruits (Solanum lycopersicum) and pomace from industrial tomato processing, Evid. Based Complement. Altern. Med. eCAM 2013 (2013), 867578, https://doi.org/10.1155/2013/867578.

[40] P. García Herrera, M.C. Sánchez-Mata, M. Cámara, Nutritional characterization of tomato fiber as a useful ingredient for food industry, Innov. Food Sci. Emerg. Technol. 11 (4) (2010) 707–711, https://doi.org/10.1016/j.ifset.2010.07.005.

[41] S. Gautam, S. Saxena, S. Kumar, Fruits and vegetables as dietary sources of Antimutagens, J. Food Chem. Nanotechnol. 2 (3) (2016) 97–114, https://doi.org/10.17756/jfcn.2016-018.

[42] X.Y. Ge, J.L. Li, X.L. Yang, A.A. Chmura, G. Zhu, J.H. Epstein, J.K. Mazet, B. Hu, W. Zhang, C. Peng, Y.J. Zhang, C.M. Luo, B. Tan, N. Wang, Y. Zhu, G. Crameri, S. Y. Zhang, L.F. Wang, P. Daszak, Z.L. Shi, Isolation and characterization of a bat SARS-like coronavirus that uses the ACE-2 receptor, Nature 503 (2013) 535–538.

[43] K. Gebeyew, G. Animut, M. Urge, T. Feyera, The effect of feeding dried tomato pomace and concentrate feed on body weight change, carcass parameter and economic feasibility on Hararghe highland sheep, eastern Ethiopia, J. Vet. Sci. Technol. 6 (2) (2015) 1, https://doi.org/10.4172/2157-7579.1000217.

[44] B. George, C. Kaur, D.S. Khurdiya, H.C. Kapoor, Antioxidants in tomato (Lycopersium esculentum) as a function of genotype, Food Chem. 84 (1) (2004) 45–51.

[45] E. Gharbi, J.P. Martínez, H. Benahmed, M.L. Fauconnier, S. Lutts, M. Quinet, Salicylic acid differently impacts ethylene and polyamine synthesis in the glycophyte Solanum lycopersicum and the wild-related halophyte Solanum chilense exposed to mild salt stress, Physiol. Plant. 158 (2) (2016) 152–167, https://doi.org/10.1111/ppl.12458.

[46] S. Gharbi, G. Renda, L. La Barbera, M. Amri, C.M. Messina, A. Santulli, Tunisian tomato by-products, as a potential source of natural bioactive compounds, Nat. Prod. Res. 31 (6) (2017) 626–631, https://doi.org/10.1080/14786419.2016.1209671.

[47] P.N. Giannelos, S. Sxizas, E. Lois, F. Zannikos, G. Anastopoulos, Physical, chemical and fuel related properties of tomato seed oil for evaluating its direct use in diesel engines, Ind. Crop. Prod. 22 (3) (2005) 193–199, https://doi.org/10.1016/j.indcrop.2004.11.001.

[48] A.M. Giuffrè, M. Capocasale, Policosanol in tomato (Solanum lycopersicum L.) seed oil: the effect of cultivar, J. Oleo Sci. 64 (6) (2015) 625–631, https://doi.org/10.5650/jos.ess15002.

[49] A.M. Giuffrè, M. Capocasale, C. Zappia, Tomato seed oil for edible use: cold break, hot break, and harvest year effects, J. Food Process. Preserv. 41 (6) (2017) 1–11, https://doi.org/10.1111/jfpp.13309.

[50] K. Gokul, Muralidhara, Oral supplements of aqueous extract of tomato seeds alleviate motor abnormality, oxidative impairments and neurotoxicity induced by rotenone in mice: relevance to Parkinson's disease, Neurochem. Res. 39 (7) (2014) 1382–1394, https://doi.org/10.1007/s11064-014-1323-1.

[51] A.E. Gorbalenya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, B.L. Haagmans, C. Lauber, A.M. Leontovich, B.W. Neuman, D. Penzar, S. Perlman, L.L.M. Poon, D.V. Samborskiy, I.A. Sidorov, I. Sola, J. Ziebuhr, The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2, Nat. Microbiol. (2020).

[52] M.H. Gordon, P. Magos, The effect of sterols on the oxidation of edible oils, Food Chem. 10 (2) (1983) 141–147, https://doi.org/10.1016/0308-8146(83)90030-4.

[53] J.L. Guil-Guerrero, R. Ramos-Bueno, I. Rodríguez-García, C. López-Sánchez, Cytotoxicity screening of several tomato extracts, J. Med. Food 14 (1–2) (2011) 40–45, https://doi.org/10.1089/jmf.2010.0051.

[54] D.P. Han, A. Penn-Nicholson, M.W. Cho, Identification of critical determinants on ACE-2 for SARS-CoV entry and development of a potententry inhibitor, Virology 350 (2006) 15–25.

[55] W.-S. He, L. Li, J. Rui, J. Li, Y. Sun, D. Cui, B. Xu, Tomato seed oil attenuates hyperlipidemia and modulates gut microbiota in C57BL/6J mice, Food Funct. 11 (5) (2020) 4275–4290, https://doi.org/10.1039/D0FO00133C.

[56] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

[57] Q. Huang, X. Wu, X. Zheng, S. Luo, S. Xu, J. Weng, Targeting inflammation and cytokine storm in COVID-19, Pharmacol. Res. 159 (2020), 105051.

[58] A. Ianevski, R. Yao, M.H. Fenstad, S. Biza, E. Zusinaite, T. Reisberg, D.E. Kainov, Potential antiviral options against SARS-CoV-2 infection, Viruses 12 (6) (2020) 642.

[59] R. Ilahy, G. Piro, I. Tlili, A. Riahi, R. Sihem, I. Ouerghi, C. Hdider, M.S. Lenucci, Fractionate analysis of the phytochemical composition and antioxidant activities in advanced breeding lines of high-lycopene tomatoes, Food Funct. 7 (1) (2016) 574–583, https://doi.org/10.1039/C5FO00553A.

[60] N. Jha, M. Jeyaraman, M. Rachamalla, S. Ojha, K. Dua, D. Chellappan, S. Muthu, A. Sharma, S. Jha, R. Jain, N. Jeyaraman, P. GS, R. Satyam, F. Khan, P. Pandey, N. Verma, S. Singh, S. Roychoudhury, S. Dholpuria, J. Ruokolainen, K. Kesari, Current understanding of novel coronavirus: molecular pathogen- esis, diagnosis, and treatment approaches, Immuno 1 (2021) 30–66.

[61] M. Jóźwiak, A. Filipowska, F. Fiorino, M. Struga, Anticancer activities of fatty acids and their heterocyclic derivatives, Eur. J. Pharmacol. 871 (2020), 172937, https://doi.org/10.1016/j.ejphar.2020.172937.

[62] C.H. Jung, I. Cho, J. Ahn, T.-I. Jeon, T.-Y. Ha, Quercetin reduces high-fat diet-induced fat accumulation in the liver by regulating lipid metabolism genes, Phytother. Res. 27 (1) (2012) 139–143, https://doi.org/10.1002/ptr.4687.

[63] G. Kaur, N. Verma, Nature curing cancer–review on structural modification studies with natural active compounds having anti-tumor efficiency, Biotechnol. Rep. 6 (2015) 64–78, https://doi.org/10.1016/j.btre.2015.01.005.

[64] J. Kermani, N. Goodarzi, M. Bakhtiari, An experimental study to evaluate the protective effects of Solanum lycopersicum seed essential oil on diabetes-induced testicular injuries, Medicina 55 (8) (2019) 499, https://doi.org/10.3390/medicina55080499.

[65] S.P. Kim, S.H. Nam, M. Friedman, The tomato glycoalkaloid α-tomatine induces caspase-independent cell death in mouse colon cancer CT-26 cells and transplanted tumors in mice, J. Agric. Food Chem. 63 (4) (2015) 1142–1150, https://doi.org/10.1021/jf5040288.

[66] G. Krishna, Muralidhara, Aqueous extract of tomato seeds attenuates rotenone-induced oxidative stress and neurotoxicity in Drosophila melanogaster, J. Sci. Food Agric. 96 (5) (2016) 1745–1755, https://doi.org/10.1002/jsfa.7281.

[67] E.Y. Lee, J.A. Yoo, S.M. Lim, K.H. Cho, Anti-aging and tissue regeneration ability of policosanol along with lipid-lowering effect in hyperlipidemic zebrafish via enhancement of high-density lipoprotein functionality, Rejuvenation Res. 19 (2) (2016) 149–158.

[68] K.R. Lee, N. Kozukue, J.S. Han, J.H. Park, E.Y. Chang, E.J. Baek, J.S. Chang, M. Friedman, Glycoalkaloids and metabolites inhibit the growth of human colon (HT29) and liver (HepG2) cancer cells, J. Agric. Food Chem. 52 (10) (2004) 2832–2839, https://doi.org/10.1021/jf030526d.

[69] B. Li, Y. Terazono, N. Hirasaki, Y. Tatemichi, E. Kinoshita, A. Obata, T. Matsui, Inhibition of glucose transport by tomatoside a, a tomato seed steroidal saponin, through the suppression of GLUT2 expression in Caco-2 cells, J. Agric. Food Chem. 66 (6) (2018) 1428–1434, https://doi.org/10.1021/acs.jafc.7b06078.

[70] W. Li, M.J. Moore, N. Vasilieva, J. Sui, S.K. Wong, M.A. Berne, M. Somasundaran, J.L. Sullivan, K. Luzuriaga, T.C. Greenough, H. Choe, M. Farzan, Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Nature 426 (2003) 450–454.

[71] K. Linnewiel-Hermoni, M. Khanin, M. Danilenko, G. Zango, Y. Amosi, J. Levy, Y. Sharoni, The anti-cancer effects of carotenoids and other phytonutrients resides in their combined activity, Arch. Biochem. Biophys. 572 (2015) 28–35, https://doi.org/10.1016/j.abb.2015.02.018.

[72] H. Liu, M. Wan, Y. Wu, Research of tomato seed oil on blood glucose, glucose tolerance and antioxidant ability in diabetic mice by alloxan, Chin. J. Ethnomed. Ethnopharm. 2017 (2017) 15.

[73] S. Liu, M.Y. Tan, S.P. Zhao, H. Rong, Effects of policosanol on serum lipids and heme oxygenase-1 in patients with hyperlipidemia, Zhonghua xin xue guan bing za zhi 40 (10) (2012) 840–843.

[74] Z. Lu, J. Wang, R. Gao, F. Ye, G. Zhao, Sustainable valorisation of tomato pomace: a comprehensive review, Trends Food Sci. Technol. 86 (2019) 172–187, https://doi.org/10.1016/j.tifs.2019.02.020.

[77] S. Maiti, A. Banerjee, Epigallocatechin gallate and theaflavin gallate interaction in SARS-CoV-2 spike-protein central channel with reference to the hydroxychloroquine interaction: bioinformatics and molecular docking study, Drug Dev. Res. 82 (1) (2021) 86–96.

[78] R. Maldonado-Torres, J.I. Morales-Camacho, F. López-Valdez, L. Huerta-González, S. Luna-Suárez, Assessment of techno-functional and nutraceutical potential of tomato (Solanum lycopersicum) seed meal, Molecules 25 (18) (2020) 4235, https://doi.org/10.3390/molecules25184235.

[79] R. Martí, S. Roselló, J. Cebolla-Cornejo, Tomato as a source of carotenoids and polyphenols targeted to cancer prevention, Cancers 8 (6) (2016) 58, https://doi.org/10.3390/cancers8060058.

[80] V.K. Maurya, S. Kumar, A.K. Prasad, M.L. Bhatt, S.K. Saxena, Structure-based drug designing for potential antiviral activity of selected natural products from Ayurveda against SARS-CoV-2 spike glycoprotein and its cellular receptor, Virusdisease 31 (2) (2020) 179–193.

[82] M. Mechmeche, F. Kachouri, H. Ksontini, M. Hamdi, Production of bioactive peptides from tomato seed isolate by Lactobacillus plantarum fermentation and enhancement of antioxidant activity, Food Biotechnol. 31 (2) (2017) 94–113, https://doi.org/10.1080/08905436.2017.1302888.

[83] M. Mechmeche, H. Ksontini, M. Hamdi, F. Kachouri, Production of bioactive peptides in tomato seed protein isolate fermented by water kefir culture: optimization of the fermentation conditions, Int. J. Pept. Res. Ther. 25 (1) (2019) 137–150, https://doi.org/10.1007/s10989-017-9655-8.

[84] N. Meshginfar, A.S. Mahoonak, F. Hosseinian, A. Tsopmo, Physicochemical, antioxidant, calcium binding, and angiotensin converting enzyme inhibitory properties of hydrolyzed tomato seed proteins, J. Food Biochem. 43 (2) (2019) 1–10, https://doi.org/10.1111/jfbc.12721.

[85] A. Milani, M. Basirnejad, S. Shahbazi, A. Bolhassani, Carotenoids: biochemistry, pharmacology and treatment, Br. J. Pharmacol. 174 (11) (2017) 1290–1324, https://doi.org/10.1111/bph.13625.

[86] A. Moayedi, M. Hashemi, M. Safari, Valorization of tomato waste proteins through production of antioxidant and antibacterial hydrolysates by proteolytic Bacillus subtilis: optimization of fermentation conditions, J. Food Sci. Technol. 53 (1) (2016) 391–400, https://doi.org/10.1007/s13197-015-1965-2.

[87] A. Moayedi, L. Mora, M.C. Aristoy, M. Hashemi, M. Safari, F. Toldrá, ACE-inhibitory and antioxidant activities of peptide fragments obtained from tomato processing by-products fermented using bacillus subtilis: effect of amino acid composition and peptides molecular mass distribution, Appl. Biochem. Biotechnol. 181 (1) (2017) 48–64, https://doi.org/10.1007/s12010-016-2198-1.

[88] A. Moayedi, L. Mora, M.C. Aristoy, M. Safari, M. Hashemi, F. Toldrá, Peptidomic analysis of antioxidant and ACE-inhibitory peptides obtained from tomato waste proteins fermented using Bacillus subtilis, Food Chem. 250 (2018) 180–187, https://doi.org/10.1016/j.foodchem.2018.01.033.

[89] S. Moco, E. Capanoglu, Y. Tikunov, R.J. Bino, D. Boyacioglu, R.D. Hall, J. Vervoort, R.C. De Vos, Tissue specialization at the metabolite level is perceived during the development of tomato fruit, J. Exp. Bot. 58 (15–16) (2007) 4131–4146, https://doi.org/10.1093/jxb/erm271.

[90] P. Mohammadi Pour, S. Fakhri, S. Asgary, M.H. Farzaei, J. Echeverria, The signaling pathways, and therapeutic targets of antiviral agents: focusing on the antiviral approaches and clinical perspectives of anthocyanins in the management of viral diseases, Front. Pharmacol. 10 (2019) 1207.

[91] L. Müller, A. Catalano, R. Simone, A. Cittadini, K. Fröhlich, V. Böhm, P. Palozza, Antioxidant capacity of tomato seed oil in solution and its redox properties in cultured macrophages, J. Agric. Food Chem. 61 (2) (2013) 346–354, https://doi.org/10.1021/jf302748z.

[92] I. Navarro-González, V. García-Valverde, J. García-Alonso, M.J. Periago, Chemical profile, functional and antioxidant properties of tomato peel fiber, Food Res. Int. 44 (5) (2011) 1528–1535.

[93] W. Ngwa, R. Kumar, D. Thompson, W. Lyerly, R. Moore, T.E. Reid, N. Toyang, Potential of flavonoid-inspired phytomedicines against COVID-19, Molecules 25 (11) (2020) 2707.

[94] A. Niedzwiecki, M.W. Roomi, T. Kalinovsky, M. Rath, Anticancer efficacy of polyphenols and their combinations, Nutrients 8 (9) (2016) 552, https://doi.org/10.3390/nu8090552.

[95] M. Noa, R. Mas, Protective effect of policosanol on atherosclerotic plaque on aortas in monkeys, Arch. Med. Res. 36 (5) (2005) 441–447.

[96] M. Noa, M. Herrera, J. Magraner, R. Más, Effect of policosanol on isoprenaline-induced myocardial necrosis in rats, J. Pharm. Pharmacol. 46 (4) (1994) 282–285.

[97] E.B. Oboulbiga, C. Parkouda, B. Savadogo, K. Traore, A.S. Traore, M.H. Dicko, Changes in physicochemical properties and bioactive compounds of tomato pulp submitted to different processing techniques, Afr. J. Food Sci. 14 (10) (2020) 330–335.

[98] Y. P. A. Silva, B.C. Borba, V.A. Pereira, M.G. Reis, M. Caliari, M.S.L. Brooks, T.A.P. C. Ferreira, Characterization of tomato processing by-product for use as a potential functional food ingredient: nutritional composition, antioxidant activity and bioactive compounds, Int. J. Food Sci. Nutr. 70 (2) (2019) 150–160, https://doi.org/10.1080/09637486.2018.1489530.

[99] I. Palomo, A. Concha-Meyer, M. Lutz, M. Said, B. Sáez, A. Vásquez, E. Fuentes, Chemical characterization and antiplatelet potential of bioactive extract from

tomato pomace (byproduct of tomato paste), Nutrients 11 (2) (2019), https://doi.org/10.3390/nu11020456.
[100] I. Palomo, E. Fuentes, T. Padró, L. Badimon, Platelets and atherogenesis: platelet anti-aggregation activity and endothelial protection from tomatoes (Solanum lycopersicum L.) (Review), Exp. Ther. Med. 3 (4) (2012) 577–584, https://doi.org/10.3892/etm.2012.477.
[101] P. Pandey, J.S. Rane, A. Chatterjee, A. Kumar, R. Khan, A. Prakash, S. Ray, Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development, J. Biomol. Struct. Dyn. (2020) 1–11.
[102] T.M. Pellicanò, V. Sicari, M.R. Loizzo, M. Leporini, T. Falco, M. Poiana, Optimizing the supercritical fluid extraction process of bioactive compounds from processed tomato skin by-products, Food Sci. Technol. 40 (2019) 692–697.
[103] A. Pérez-Gálvez, I. Viera, M. Roca, Carotenoids and chlorophylls as antioxidants, Antioxidants 9 (6) (2020) 505, https://doi.org/10.3390/antiox9060505.
[104] J. Pinela, M.A. Prieto, A.M. Carvalho, M.F. Barreiro, M.B.P.P. Oliveira, L. Barros, I.C.F.R. Ferreira, Microwave-assisted extraction of phenolic acids and flavonoids and production of antioxidant ingredients from tomato: a nutraceutical-oriented optimization study, Sep. Purif. Technol. 164 (2016) 114–124, https://doi.org/10.1016/j.seppur.2016.03.030.
[105] K.L. Platt, R. Edenharder, S. Aderhold, E. Muckel, H. Glatt, Fruits and vegetables protect against the genotoxicity of heterocyclic aromatic amines activated by human xenobiotic-metabolizing enzymes expressed in immortal mammalian cells, Mutat. Res. Genet. Toxicol. Environ. Mutagen. 703 (2) (2010) 90–98, https://doi.org/10.1016/j.mrgentox.2010.08.007.
[106] L. Previtera, G. Fucci, A. De Marco, V. Romanucci, G. Di Fabio, A. Zarrelli, Chemical and organoleptic characteristics of tomato purée enriched with lyophilized tomato pomace, J. Sci. Food Agric. 96 (6) (2016) 1953–1958, https://doi.org/10.1002/jsfa.7303.
[107] A. Raiola, M.M. Rigano, R. Calafiore, L. Frusciante, A. Barone, Enhancing the health-promoting effects of tomato fruit for biofortified food, Mediat. Inflamm. 2014 (2014), 139873, https://doi.org/10.1155/2014/139873.
[108] R. Rauscher, R. Edenharder, K.L. Platt, In vitro antimutagenic and in vivo anticlastogenic effects of carotenoids and solvent extracts from fruits and vegetables rich in carotenoids, Mutat. Res. Genet. Toxicol. Environ. Mutagen. 413 (2) (1998) 129–142, https://doi.org/10.1016/S1383-5718(98)00017-5.
[109] D. Richard, K. Kefi, U. Barbe, P. Bausero, F. Visioli, Polyunsaturated fatty acids as antioxidants, Pharmacol. Res. 57 (6) (2008) 451–455.
[110] R. Rodríguez-Azúa, A. Treuer, R. Moore-Carrasco, D. Cortacáns, M. Gutiérrez, L. Astudillo, E. Fuentes, I. Palomo, Effect of tomato industrial processing (different hybrids, paste, and pomace) on inhibition of platelet function in vitro, ex vivo, and in vivo, J. Med. Food 17 (4) (2014) 505–511, https://doi.org/10.1089/jmf.2012.0243.
[111] D.B. Rodriguez, T.-C. Lee, C.O. Chichester, Comparative study of the carotenoid composition of the seeds of ripening Momordica charantia and tomatoes, Plant Physiol. 56 (5) (1975) 626–629, https://doi.org/10.1104/pp.56.5.626.
[112] N. Roshanravan, F. Seif, A. Ostadrahimi, M. Pouraghaei, S. Ghaffari, Targeting cytokine storm to manage patients with COVID-19: a mini-review, Arch. Med. Res. 51 (7) (2020) 608–612.
[113] A. Ruiz Celma, F. Cuadros, F. López-Rodríguez, Characterisation of industrial tomato by-products from infrared drying process, Food Bioprod. Process. 87 (4) (2009) 282–291, https://doi.org/10.1016/j.fbp.2008.12.003.
[114] M.G. Saklayen, The global epidemic of the metabolic syndrome, Curr. Hypertens. Rep. 20 (2) (2018) 1–8, https://doi.org/10.1007/s11906-018-0812-z.
[115] B. Salehi, R. Sharifi-Rad, F. Sharopov, J. Namiesnik, A. Roointan, M. Kamle, P. Kumar, N. Martins, J. Sharifi-Rad, Beneficial effects and potential risks of tomato consumption for human health: an overview, Nutrition 62 (2019) 201–208, https://doi.org/10.1016/j.nut.2019.01.012.
[116] A. Sarkar, P. Kaul, Evaluation of tomato processing by-products: a comparative study in a pilot scale setup, J. Food Process Eng. 37 (3) (2014) 299–307, https://doi.org/10.1111/jfpe.12086.
[117] S. Seltzer, Linking ACE2 and angiotensin II to pulmonary immunovascular dysregulation in SARS-CoV-2 infection, Int. J. Infect. Dis. 101 (2020) 42–45.
[118] D. Shao, G.G. Atungulu, Z. Pan, T. Yue, A. Zhang, Z. Fan, Characteristics of isolation and functionality of protein from tomato pomace produced with different industrial processing methods, Food Bioprocess Technol. 7 (2) (2014) 532–541, https://doi.org/10.1007/s11947-013-1057-0.
[119] D. Shao, G.E. Bartley, W. Yokoyama, Z. Pan, H. Zhang, A. Zhang, Plasma and hepatic cholesterol-lowering effects of tomato pomace, tomato seed oil and defatted tomato seed in hamsters fed with high-fat diets, Food Chem. 139 (1) (2013) 589–596, https://doi.org/10.1016/j.foodchem.2013.01.043.
[120] D. Shao, C. Venkitasamy, X. Li, Z. Pan, J. Shi, B. Wang, H.E. Teh, T.H. McHugh, Thermal and storage characteristics of tomato seed oil, LWT Food Sci. Technol. 63 (1) (2015) 191–197, https://doi.org/10.1016/j.lwt.2015.03.010.
[121] R. Sharma, T. Matsuzaka, M.K. Kaushik, T. Sugasawa, H. Ohno, Y. Wang, H. Shimano, Octacosanol and policosanol prevent high-fat diet-induced obesity and metabolic disorders by activating brown adipose tissue and improving liver metabolism, Sci. Rep. 9 (1) (2019) 1–12.
[122] Y. Shi, B. Zhang, X.-J. Chen, D.-Q. Xu, Y.-X. Wang, H.-Y. Dong, S.R. Ma, R.H. Sun, Y.P. Hui, Z.C. Li, Osthole protects lipopolysaccharide-induced acute lung injury inmice by preventing down-regulation of angiotensin-converting enzyme 2, Eur. J. Pharm. Sci. 48 (4–5) (2013) 819–824, https://doi.org/10.1016/j.ejps.2012.12.031.
[123] W.W. So, W.N. Liu, K.N. Leung, Omega-3 polyunsaturated fatty acids trigger cell cycle arrest and induce apoptosis in human neuroblastoma LA-N-1 cells, Nutrients 7 (2015) 6956–6973, https://doi.org/10.3390/nu7085319.
[124] S. Solomon, W. Mulugeta, Disease burden and associated risk factors for metabolic syndrome among adults in Ethiopia, BMC Cardiovasc. Disord. 19 (1) (2019) 236, https://doi.org/10.1186/s12872-019-1201-5.
[125] M. Soy, G. Keser, P. Atagündüz, F. Tabak, I. Atagündüz, S. Kayhan, Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment, Clin. Rheumatol. 39 (2020) 2085–2094.
[126] W. Stahl, W. Schwarz, A.R. Sundquist, H. Sies, Cis-trans isomers of lycopene and β-carotene in human serum and tissues, Arch. Biochem. Biophys. 294 (1) (1992) 173–177.
[127] S. Stajčić, G. Ćetković, J. Čanadanović-Brunet, S. Djilas, A. Mandić, D. Četojević-Simin, Tomato waste: carotenoids content, antioxidant and cell growth activities, Food Chem. 172 (2015) 225–232, https://doi.org/10.1016/j.foodchem.2014.09.069.
[128] K. Szabo, Z. Diaconeasa, A.F. Cătoi, D.C. Vodnar, Screening of ten tomato varieties processing waste for bioactive components and their related antioxidant and antimicrobial activities, Antioxidants 8 (8) (2019) 292, https://doi.org/10.3390/antiox8080292.
[129] K. Szabo, F.V. Dulf, Z. Diaconeasa, D.C. Vodnar, Antimicrobial and antioxidant properties of tomato processing byproducts and their correlation with the biochemical composition, LWT 116 (2019), https://doi.org/10.1016/j.lwt.2019.108558.
[130] K. Szabo, F.V. Dulf, B.E. Teleky, P. Eleni, C. Boukouvalas, M. Krokida, D. C. Vodnar, Evaluation of the bioactive compounds found in tomato seed oil and tomato peels influenced by industrial heat treatments, Foods 10 (1) (2021) 110.
[131] H.-L. Tan, J.M. Thomas-Ahner, E.M. Grainger, L. Wan, D.M. Francis, S. J. Schwartz, Jr Erdman JW, S.K. Clinton, Tomato-based food products for prostate cancer prevention: what have we learned? Cancer Metastasis Rev. 29 (3) (2010) 553–568, https://doi.org/10.1007/s10555-010-9246-z.
[132] M. Taveira, L.R. Silva, L.A. Vale-Silva, E. Pinto, P. Valentão, F. Ferreres, P. Guedes de Pinho, P.B. Andrade, Lycopersicon esculentum Seeds: an industrial byproduct as an antimicrobial agent, J. Agric. Food Chem. 58 (17) (2010) 9529–9536, https://doi.org/10.1021/jf102215g.
[133] G. Tommonaro, A. Caporale, L. De Martino, A. Popolo, R. De Prisco, B. Nicolaus, G.R. Abbamondi, C. Saturnino, Antioxidant and cytotoxic activities investigation of tomato seed extracts, Nat. Prod. Res. 28 (10) (2014) 764–768, https://doi.org/10.1080/14786419.2013.879474.
[134] R.K. Toor, G.P. Savage, Antioxidant activity in different fractions of tomatoes, Food Res. Int. 38 (5) (2005) 487–494, https://doi.org/10.1016/j.foodres.2004.10.016.
[135] O. Torres, A.J. Agramonte, J. Illnait, R.M. Ferreiro, L. Fernández, J.C. Fernández, Treatment of hypercholesterolemia in NIDDM with policosanol, Diabetes Care 18 (3) (1995) 393–397, https://doi.org/10.2337/diacare.18.3.393.
[136] N. Tsantila, H.C. Karantonis, D.N. Perrea, S.E. Theocharis, D.G. Iliopoulos, C. Iatrou, S. Antonopoulou, C.A. Demopoulos, Atherosclerosis regression study in rabbits upon olive pomace polar lipid extract administration, Nutr. Metab. Cardiovasc. Dis. 20 (10) (2010) 740–747, https://doi.org/10.1016/j.numecd.2009.06.008.
[137] M. Valdez-Morales, L.G. Espinosa-Alonso, L.C. Espinoza-Torres, F. Delgado-Vargas, S. Medina-Godoy, Phenolic content and antioxidant and antimutagenic activities in tomato peel, seeds, and byproducts, J. Agric. Food Chem. 62 (23) (2014) 5281–5289, https://doi.org/10.1021/jf5012374.
[138] A.F. Vinha, R.C. Alves, S.V.P. Barreira, A. Castro, A.S.G. Costa, M.B.P.P. Oliveira, Effect of peel and seed removal on the nutritional value and antioxidant activity of tomato (Lycopersicon esculentum L.) fruits, LWT Food Sci. Technol. 55 (1) (2014) 197–202, https://doi.org/10.1016/j.lwt.2013.07.016.
[139] C. Vissiennon, K. Nieber, O. Kelber, V. Butterweck, Route of administration determines the anxiolytic activity of the flavonols kaempferol, quercetin and myricetin—are they prodrugs? J. Nutr. Biochem. 23 (7) (2012) 733–740.
[140] M. Viuda-Martos, E. Sanchez-Zapata, E. Sayas-Barberá, E. Sendra, J.A. Pérez-Álvarez, J. Fernández-López, Tomato and tomato byproducts. human health benefits of lycopene and its application to meat products: a review, Crit. Rev. Food Sci. Nutr. 54 (8) (2014) 1032–1049, https://doi.org/10.1080/10408398.2011.623799.
[141] Y. Wang, M.A. Berhow, M. Black, E.H. Jeffery, A comparison of the absorption and metabolism of the major quercetin in brassica, quercetin-3-O-sophoroside, to that of quercetin aglycone, in rats, Food Chem. 311 (2020), 125880.
[142] L. Yonekura, A. Nagao, Intestinal absorption of dietary carotenoids, Mol. Nutr. Food Res. 51 (1) (2007) 107–115.
[143] W. Yu, L. Jia, S.-K. Park, J. Li, A. Gopalan, M. Simmons-Menchaca, B.G. Sanders, K. Kline, Anticancer actions of natural and synthetic vitamin E forms: RRR-alpha-tocopherol blocks the anticancer actions of gamma-tocopherol, Mol. Nutr. Food Res. 53 (12) (2009) 1573–1581, https://doi.org/10.1002/mnfr.200900011.
[144] H. Zieliński, H. Kozłowska, Antioxidant activity and total phenolics in selected cereal grains and their different morphological fractions, J. Agric. Food Chem. 48 (6) (2000) 2008–2016, https://doi.org/10.1021/jf990619o.
[145] P. Zimmet, K. Alberti, N. Stern, C. Bilu, A. El-Osta, H. Einat, N. Kronfeld-Schor, The Circadian syndrome: is the metabolic syndrome and much more!, J. Intern. Med. 286 (2) (2019) 181–191, https://doi.org/10.1111/joim.12924.